Current Cardiovascular Risk Reports (2019) 13: 12
https://doi.org/10.1007/s12170-019-0610-4

SECONDARY PREVENTION AND INTERVENTION (D. STEINBERG, SECTION EDITOR)

Transcatheter Mitral Valve Therapy: Repair and Replacement

Marvin H. Eng [1] · **Tiberio Frisoli** [1] · **Dee Dee Wang** [1] · **William W. O'Neill** [1]

Published online: 24 April 2019

Abstract

Purpose of Review In this paper, we discuss the salient clinical and anatomic challenges in percutaneous mitral valve repair and replacement.

Recent Findings The mitral valve is complex structure and understanding its intricacies and anatomic relationships to surrounding structures (i.e., aortic valve and papillary muscles) is central to delivery of therapies. Part of the complexity is treatment of primary and secondary mitral regurgitation, where in primary regurgitation the valve is the primary issue and treatment should be curative or treatment of secondary mitral regurgitation, where the valve is subject to distortion due to adverse myocardial remodeling (i.e. myocardial infarction or dilated cardiomyopathy). Percutaneous edge-to-edge mitral valve repair remains the current standard of non-surgical therapy and while thousands of patients have been treated, limitations related to leaflet calcification, mitral valve annular area, and large flail gaps remain as challenges in using this device. Alternative annuloplasty-based devices can work either through implanting anchors in the annular tissue or via the coronary sinus. New artificial chordae tendineae are a promising therapy for flail leaflets. Transcatheter mitral valve replacement has even more challenges with respect to potential left ventricular outflow tract obstruction, valve fixation, and the requirement for oral anti-coagulation for thromboprophylaxis.

Summary Transcatheter therapy for repair or replacement of the mitral valve remains in early stages, and delineating a strategy for selecting the proper devices and patients for either repair or replacement will be a major focus in the years forthcoming.

Keywords Mitral valve regurgitation · Computed tomography · 3D echocardiography · Percutaneous mitral valve repair · Percutaneous mitral valve replacement · Left ventricular outflow tract obstruction

Introduction

Moderate to severe mitral valvular disease has a prevalence of 9–10% in patients ≥ 75 years, greater than double that aortic valve disease [1]. Over 4% of patients in the same age group have isolated mitral regurgitation (MR) [2•]. The presence of primary or secondary mitral regurgitation differs in selected studies, but recent analysis of an echocardiographic registry showed approximately 55% of patients have primary MR, 30% secondary MR, while 14% have a mixed etiology [3]. Innovation in transcatheter mitral valve therapies has been developed to treat the aging population, and as a result, multiple devices have been developed for both repair and valve replacement [4, 5]. The compounding of complex mitral valve anatomy, multiple options for repair/replacement, and the issues of elderly patients make mitral therapy a challenging frontier.

This article is part of Topical Collection on *Secondary Prevention and Intervention*

✉ Marvin H. Eng
meng1@hfhs.org

Tiberio Frisoli
tfrisoli1@hfhs.org

Dee Dee Wang
dwang2@hfhs.org

William W. O'Neill
woneill1@hfhs.org

[1] Center for Structural Heart Disease, Structural Heart Disease Fellowship Director, Director of Research for the Center for Structural Heart Disease, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, MI 48202, USA

Anatomy of the Mitral Valve

The mitral valve (MV) is composed of two leaflets, annular attachment at the atrioventricular junction, tendinous cords, and papillary muscles (Fig. 1). The two leaflets are clinically described as anterior and posterior; however, anatomists have also

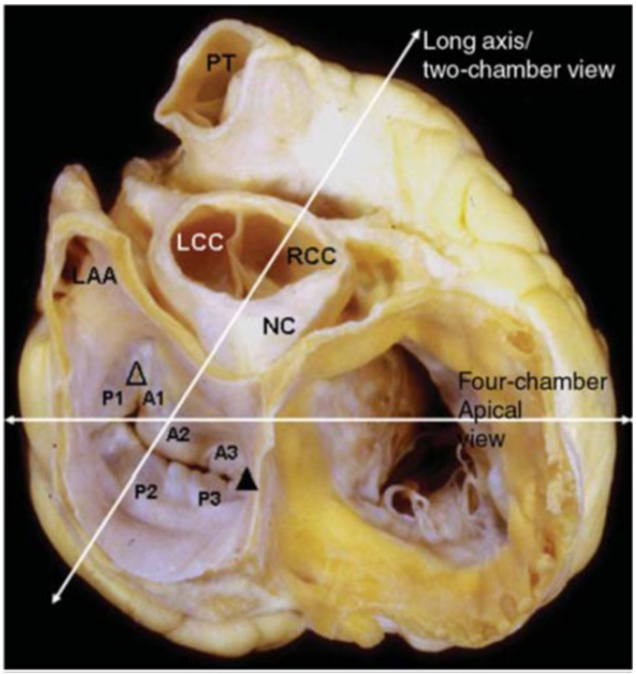

Fig. 1 Mitral valve anatomy from the perspective of the left atrium. The anterolateral commissure (Δ) is adjacent to the left atrial appendage (LAA), and the line of coaptation extends in a curved line towards the interatrial septum ending at the posteromedial commissure (Δ). The anterior leaflet (A1–A3) abuts the aortic valve while the posterior leaflet (P1–3) attaches to the posterior myocardium. Using the Carpentier system, the most lateral is termed "1" and most medial segments of each leaflet is "3". (Figure adapted from McCarthy, K.P. et al. Eur J of Echocardiography 2010;11:i3-i9) [9]

used the terms aortic and mural respectively [6•]. The anterior leaflet comprises one-third of the annular circumference and has a fibrous continuity with the left and non-coronary cusps of the aortic valve as well as the interleaflet triangle between the cusps that abuts onto the membranous septum [6•, 7]. Carpentier's nomenclature describes the most lateral segment as A1, A2 is central, and the A3 is the medial segment [8]. The posterior leaflet extends two-thirds around the left atrioventricular junction within the inlet portion of the ventricle and is not as broad as the anterior leaflet. The posterior leaflet has indentations that generally form three scallops along the line of coaptation. Carpentier's system again describes the most lateral segment of the posterior leaflet as P1 and the most medial as P3.

The annulus is the junctional zone that distinguishes the left atrium and ventricle, also giving attachment to the mitral valve. As a pliable structure, it is not a rigid fibrous ring and changes shape during the cardiac cycle. In oval or "D" shaped, the commissure-to-commissure diameter is wider than the anteroposterior diameter. The anterior leaflet and both trigones are in fibrous continuity with the aortic valve as mentioned previously. This portion of the annulus is more fibrous and less prone to dilation. The remaining two-thirds of the annulus is muscular and is subject to dilation and more prone to calcification.

Leaflets have fan-shaped chordal attachments connecting leaflets to the papillary muscles. Depending on the location of the attachment, there are three types of chordae tendineae [9]. Primary chords attach the free edge of the leaflet body to papillary muscles. Secondary chords attach to the ventricular surface of valve, in the region of the leaflet body closer to middle of the valve. Tertiary chords are found only on the posterior leaflet and attach to the ventricular wall. The posteromedial papillary muscle supplies chords to the medial half of both leaflets; this includes the posteromedial commissure, P3, A3, and medial half of A2/P2. Similarly, the anterolateral papillary muscle chords attach to the lateral half of both leaflets (i.e., anterolateral commissure, A1, P1, and half of P2/A2). Two of the anterior leaflet cords are larger and thicker than the rest; these arise from the tip of each papillary muscle and are termed strut cords.

The papillary muscles are generally located in the anterolateral and posteromedial positions at the mid to apical segments of the left ventricle. The posteromedial papillary muscle can have up to three heads in adults [10]; however, the distribution of papillary muscle can vary significantly, particularly in the context of myxomatous mitral valve disease. Some cases, one or both papillary muscles are undefinable and replaced with multiple small muscled bundles.

Abnormal Mitral Valve Function

Successful function of the leaflets depends on complete coaptation and apposition of the leaflets to prevent regurgitation. While there is not one classification system that completely describes the mode of failure, two major systems are commonly used and may serve as a starting point. Societal guidelines from the American College of Cardiology and American Heart Association classify mitral regurgitation as primary (degenerative) and secondary (functional) [11]. Primary MR refers to pathology of ≥ 1 of the valve (leaflets, chordae, papillary muscle, annulus) to be the cause of incompetence. Should the mitral regurgitation continue, subsequent volume overload will cause myocardial damage, heart failure, and eventual death; therefore, correction of the mitral valve is considered curative. However, in secondary mitral regurgitation, the valve is normal and the myocardium is diseased usually either from ischemic heart disease (i.e., myocardial infarction) or a myopathy of various etiologies (i.e., viral, genetic, idiopathic) causing displacement of papillary muscles. Associated tethering and annular dilation from the primary myocardial disease cause MR; however, valve incompetence is only one component of heart failure. Addressing the valve does not correct the remaining disease processes such as coronary disease or myopathy, thus fixing the valve is not curative. Progression of the cardiomyopathy may compromise the outcomes of valve therapies.

In addition to primary and secondary is the Carpentier's system for describing mitral valve pathology relative to mitral annular plane and is commonly used (Fig. 2). Type 1 describes normal leaflet motion, and the MR is a result of etiologies such as leaflet perforation or annular dilation from atrial fibrillation. Type 2 describes excessive leaflet motion above the annular plane usually from leaflet prolapse. Type 3 is leaflet restriction, and there are two subtypes. Type 3a is restriction of leaflet motion in both systole and diastole (i.e., rheumatic disease), while 3b is restriction in systole only (ischemic heart disease or dilated cardiomyopathy) [8].

Anatomic Considerations for Valve Therapy

The range of transcatheter mitral valve devices is diverse, each with its particular limitations [5]. In general, there are devices for either repair or replacement and we will attempt to point out the limitations of each strategy. The goal of achieving a significant reduction in mitral regurgitation is paramount as data shows that patients undergoing unsuccessful repair with residual significant mitral regurgitation in USA and European registries are prognostically poor [12–14]. Procedure failure in a multi-center German registry was associated with a 4.36-fold increase in 1-year mortality, exemplifying the importance of efficacious reduction of MR [14].

Anatomic Considerations for Valve Therapy

Edge-to-Edge Valvular Repair

Current generation edge-to-edge repair devise including the MitraClip (Abbott) and the PASCAL device (Edwards Lifesciences) are both based on the Alfieri principle of binding the leaflets together at the point of mal-coaptation [15, 16]. Edge-to-edge repair was initially tested against surgery in treating primary (degenerative) mitral regurgitation in the EVEREST II trial [15]. While able to reduce mitral regurgitation, MitraClip was initially found to be inferior to surgery for durable reduction of mitral regurgitation as more MitraClip patients required surgery post-implantation (MitraClip 20% vs. surgery 2%, $p < 0.001$). Although initial MR reduction in MitraClip patients was less that surgery, from the 6 month time point out to 5 years, MitraClip and surgery had comparable rates of recurrent MR and repeat surgery showing that a good MitraClip result has reasonable 5-year durability [17]. Ultimately, the FDA recognized the merits of percutaneous mitral valve repair and approved the device for commercial using in the USA in patients with primary MR who are prohibitive risk for surgery.

Given the various investigational devices for reduction of MR, patient selection for edge-to-edge repair continues to be refined. Recent analysis regarding optimal hemodynamic response with edge-to-edge repair showed that flail scallop and single jets have a 3.49 (1.40–9.15)- and 3.56 (1.24–11.98)-fold increase in left atrial pressure reduction respectively [18•]. Patients conforming to the Endovascular Valve Edge-To-Edge Repair Study (EVEREST) criteria (Table 1) are reportedly to have lower rates of re-intervention. When EVEREST guidelines are violated and flail gaps > 10 mm or flail width > 15 mm are treated, a trend towards to reintervention was found [19]. Furthermore, post-procedure transmitral gradients of > 5 mm are associated with a 2.3-fold increase in the combined endpoint of mortality, LV assist device, surgical mitral valve replacement, and redo procedure [20]. The findings of elevated gradients with residual mitral regurgitation are reproducibly associated with recurrent heart failure and poor outcome [21]. Operators should be alarmed at the presence of thickened immobile leaflets, calcium, or small mitral orifice and considered the ramifications of incomplete repair or high post-implant gradients (Fig. 3).

Previously, use for MitraClip for secondary MR was controversial due to the unknown survival of attempting to decrease MR without altering the cardiomyopathy. Retrospective data from several registries showed early promise in MR reduction associated with ventricular remodeling with symptom improvement [16, 22, 23]. Recently, edge-to-edge repair in the COAPT

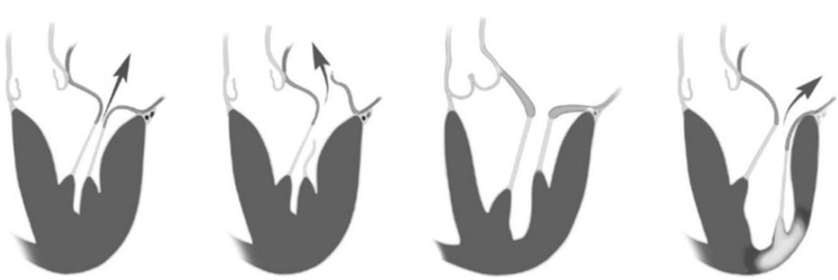

Fig. 2 Carpentier's system for describing mitral valve pathology. (1) Type 1 describes normal leaflet motion and the mitral regurgitation and includes pathology such as mitral leaflet perforation or annular dilation from atrial fibrillation. (2) Type 2 is excessive leaflet motion above the annular plane typically from leaflet prolapse. (3) Type 3 is leaflet restriction and there are 2 subtypes. Type 3a is restriction of leaflet motion in both systole and diastole (i.e., rheumatic disease), and 3b is restriction in systole only (ischemic heart disease or dilated cardiomyopathy). (Figure adapted from Filsoufi F. and Carpentier A. Principle in Reconstructive Surgery in Degenerative Mitral Valve Disease. Seminars in Thoracic and Cardiovascular Surgery 2007;19:103–10) [8]

Table 1 Endovascular Valve Edge-To-Edge Repair Study (EVEREST) criteria for Mitra-Clip implantation

EVEREST criteria for eligibility for edge-to-edge mitral valve repair
Coaptation length ≥ 2 mm
Coaptation depth < 11 mm
Flail gap < 10 mm
Flail width < 15 mm
Mitral valve area < 4 cm^2
LVEF > 25%
LVESD ≤ 55 mm

trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) showed decrease hospitalization rates and mortality when compared to optimized medical therapy (2-year hospitalization rate MitraClip 35.8% vs. medical therapy 67.9% per patient year $p < 0.001$). Currently, the approved indication for edge-to-edge repair in the USA is for primary mitral regurgitation but approval of MitraClip for secondary MR may be forthcoming based on the COAPT results.

Percutaneous Mitral Annuloplasty

The concept that the mitral annulus needs to be modified to improve valve coaptation and support the leaflets during repair resulted in surgical annuloplasty and several percutaneous devices have been developed to apply this concept in percutaneous repair. With the intention of reducing anterior-posterior annular dimensions to improve valve coaptation, devices undergoing investigation include coronary sinus cinching devices, annular anchoring devices, and devices that reducing annular anterior-posterior dimension via external tethering [5]. In devices implanted in the coronary sinus, the coronary vessel to sinus reducer relationship is critical. Carillion device (Cardiac Dimensions) implantations demonstrated circumflex branch compromise with a reducer can result in myocardial infarction [24, 25, 26•]. The mitral valve cerclage (National Institutes of Health) has a mechanism to avoid circumflex branches with curved sinus reducer and avoid trapping coronary vessels [27]. Similarly, annuloplasty devices that require anchors necessitate rigorous anatomic screening for circumflex artery proximity as well as annular calcification to allow anchor fixation (Fig. 4) [28]. These devices remain investigational in the USA.

Transcatheter Chordal Implantation

Another method for re-establishing mitral valve competency for prolapsing valves is restoring valve coaptation using artificial chords. A popular surgical technique, implantation of neochords through a small thoracotomy using echocardiographic guidance,

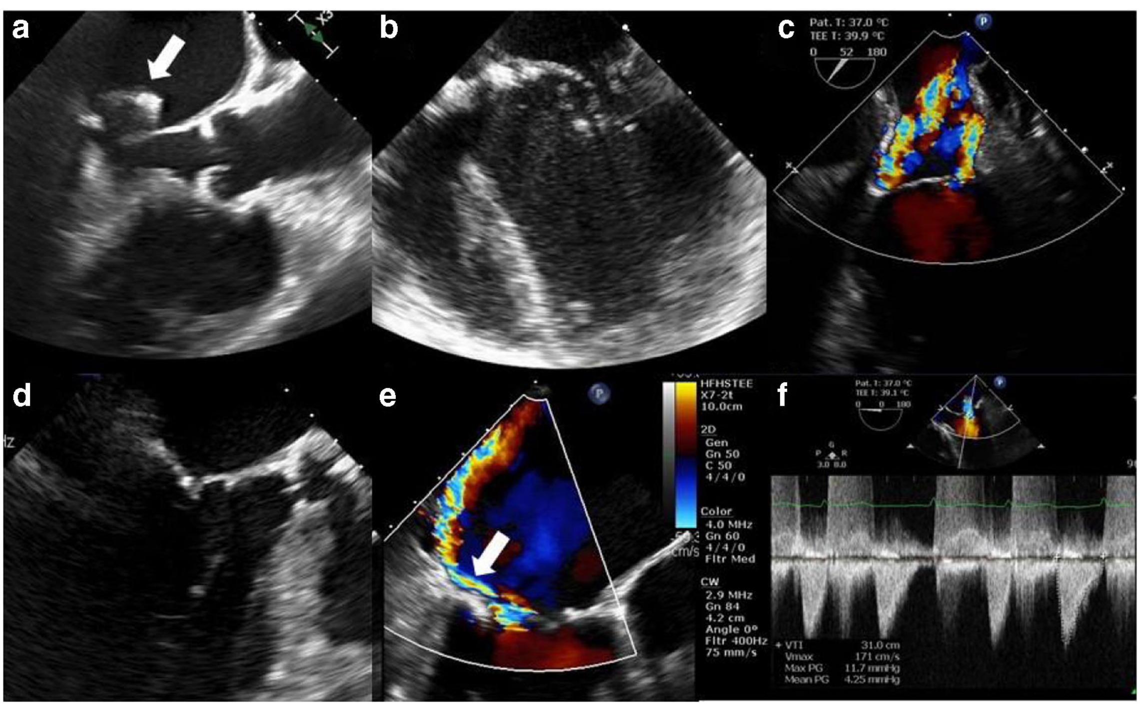

Fig. 3 Impediments to edge-to-edge leaflet repair. **a** Significant flail gap in a patient with a posterior flail (arrow). **b** Severe degenerated valve (Barlow's). **c** Multiple significant jets present. **d** Thickened and calcified leaflets alerting implanters to the possibility of elevated post-implantation gradients. **e** Thickened and calcified posterior leaflet (arrow). **f** Elevated baseline gradient of 4.5 mmHg. Elevated baseline gradients portend to high likelihood of high residual post-implant gradients. (Adapted from Eng, M and Wang DD. Current Curr Cardiol Rep 2018;20:107) [47]

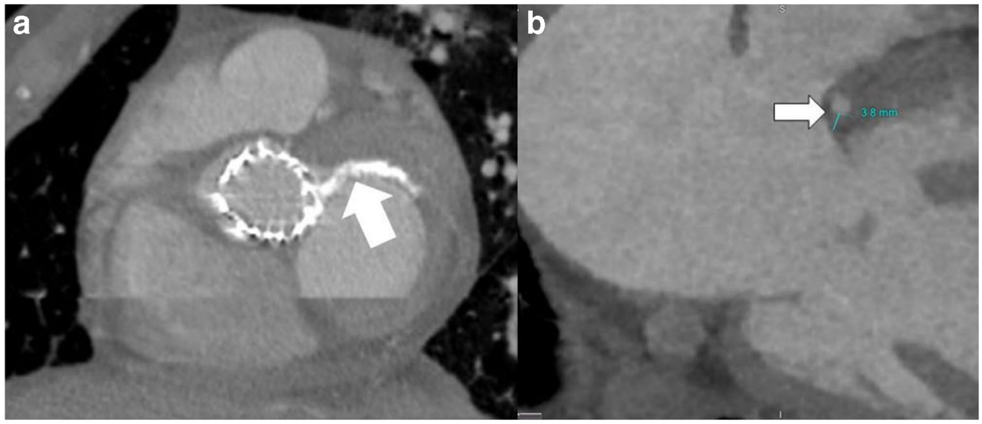

Fig. 4 Anatomic barriers to using an annular anchoring system. **a** Mitral annular calcification. **b** Close proximity of the left circumflex artery (arrow) to the mitral annulus. (Adapted from Eng, M and Wang DD. Current Curr Cardiol Rep 2018;20:107)

has been developed and now tested in the TRACER (Mitral TransApical NeoCordal Echo-Guided Repair) study using the Harpoon device (Harpoon Medical Inc.) mitral valve repair system in 30 patients [29]. The neochords are meant to tether the posterior leaflet and anchor externally to the anterior wall. Three of 30 patients required conversion to cardiac surgery and at 6 months 4/26 patients (16%) had ≥ moderate mitral regurgitation. A pivotal trial is underway.

Transcatheter Mitral Valve Replacement

While mitral valve repair is well established, some valve pathology is inappropriate for current repair techniques and replacing the entire valve is more likely to improve patient symptoms. Due to differing valve designs, screening for anatomic suitability requires an analysis of access, valve fixation, left ventricular outflow tract (LVOT) obstruction risk, and anti-coagulation requirements. The mitral valve prostheses in development currently in pivotal studies are transapically delivered, although some transseptally delivered valves are under development [4]. Large sheaths (i.e., 36 French) are still required for transapical delivery, and historical data from transcatheter aortic valve replacement should give operators pause about the morbidity associated with transapical access [30–32]. Prospective studies that included transapical access observed higher rates of early mortality, and while it was suspected that co-morbidities accounted for the difference in mortality, a propensity-matched comparison to transfemoral patients found a higher rate of renal failure, bleeding, increased length of stay, and death [32]. Rates for myocardial injury were higher in transapical cases and analysis of the extent of damage in these patients showed a greater than 2-fold increase in CK-MB 24 h post-procedure [33]. More importantly, cannulating the apex using large sheaths and disrupting myocardial architecture may be detrimental for patients with cardiomyopathy. Additionally, chronic lung disease and frailty are patients' factors making even small thoracotomies a dangerous venture due to their inability to cope with chest invasion [34]. Transseptal valves in clinical development

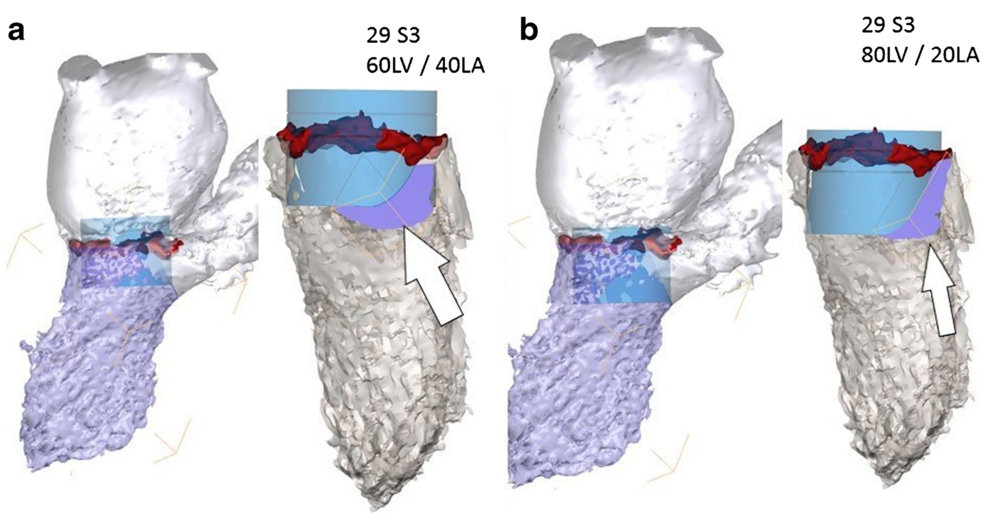

Fig. 5 Use of computed tomography (CT) and computer aided design (CAD) to predict left ventricular outflow tract obstruction (LVOT). **a** Simulation of a 29-mm Edwards Sapien S3 valve and degree of encroachment on the LVOT. Residual LVOT at a placement of 60% ventricular; 40% atrial was 123.4 mm^2. **b** Simulation using the same valve with an 80% ventricular; 40% atrial placement was found to predict a "neo-LVOT" of 99.6 mm^2. (Adapted from Eng, M and Wang DD. Current Curr Cardiol Rep 2018;20:107)

that utilize transfemoral access include the Sapien M3 system (Edwards Lifesciences) and the Caisson Valve (LivaNova), but these prostheses remain in early feasibility trials.

The anatomic substrate for mitral valve fixation is more complex than that of the aortic valve due to the less rigid, D-shaped, dynamic nature of the mitral annulus [4]. Several mechanisms of fixation are being explored: (1) countertraction to a distal constraint, such as an apical tether (Tendyne Valve, Abbott Vascular); (2) anchors to grasp the free margins of the native leaflets (TIARA, Neovasc); (3) atrial and ventricular fixation via flanges that engage the mitral annulus and leaflets/chordal apparatus (CardiacQ, Edwards); (4) anchors around the edge of the valve that pierce or provide friction with the mitral valve tissue (NaviGate Cardiac Structures); (5) radial force along the valve stent (Intrepid valve, Medtronic); and (6) use of a subannular ring or docking system for valve implantation (M3, Edwards Lifesciences). The challenge is not only prosthesis stability but also valve sealing to prevent paravalvular leak; a dominant mechanism for anchoring has yet to be determined.

Anatomic eligibility encompasses yet another complex challenge, evaluation for possible left ventricular outflow tract obstruction (LVOTO) (Fig. 5). Early experience of off-label Sapien valve use for transcatheter mitral valve replacement (TMVR) predated the use of extensive CT analysis and screening and operators discovered the first cases of LVOTO when anterior mitral leaflet is displaced towards the LVOT causing hemodynamic obstruction [35•]. These early events stimulated multi-center collaboration, and in an analysis of 38 cases of LVOTO, a predicted neo-LVOT of $\leq 189.4\ mm^2$ had 100% sensitivity and 96.8% sensitivity LVOT gradient increase post-TMVR [35•]. LVOTO is predicated on LV mass, geometry, and prosthesis dimensions. Even abnormally, long anterior mitral leaflets have interfered with prosthetic leaflet functioning [36]. Recently, a technique to intentionally lacerate the anterior mitral leaflet circumventing LVOT obstruction has been developed and publication of the early results demonstrated its feasibility [37]. Outside of intentional anterior leaflet laceration, alcohol septal ablation has been used to modify neo-LVOT to rescue from LVOTO and to prevent LVOTO by attempting to remodel the LVOT weeks prior to valve implantation [38].

Several case reports of transcatheter mitral valve thrombosis have been reported and may be a larger problem as the technology disseminates [39–42]. Transcatheter implantation is similar to leaflet and chordal sparing surgical valve replacement, and single-center surgical registry data found a 6% rate of valve thrombosis ($n = 149$). Interestingly, the cohort with native valve preservation was found to have a 24% rate of valve thrombosis in a mean time of 11.9 ± 10.6 months [43]. Recent Mitraclip data found that two-thirds of bleeding episodes were not related to vascular access, and bleeding was associated with elevated mortality rates [44]. Requirements for anti-coagulation remain undefined but may restrict the use of TMVR in patients with high bleeding risk.

One unique but pervasive clinical entity requires addressing: mitral valve regurgitation or stenosis due to mitral annular calcification (MAC). These patients often have mixed valvular stenosis and regurgitation that may difficult to repair. Even surgical replacement is fraught with a mortality as high as 5%; sometimes, injury to the posterior annulus necessitates patch repair [45]. Many MAC patients are denied surgery but the presence of calcium makes the patients poor candidates for edge-to-edge repair. Bulky annular and subannular calcifications have been implicated in perivalvular leaking with TMVR. Nevertheless, implantation of balloon expandable Edwards Sapien valves (Edwards Lifesciences, Irvine, CA) in MAC resulted in a 30-day and 1-year mortality of 25 and 53.7% respectively [46]. Impressively, 1-year echocardiography data of surviving patients showed trace or no mitral regurgitation in 75% of patients, suggesting that transcatheter valve replacement may be feasible in patients with MAC but these patients are burdened with multiple co-morbid illnesses and are certainly poor operative candidates should the transcatheter procedure fail. Patients with MAC often have small ventricles, and it remains to be seen if patients with MAC would be suitable for dedicated transcatheter mitral valves.

Conclusion

Transcatheter mitral valve interventions require an intimate understanding of the complexities of mitral valve anatomy and function. Through a multi-disciplinary approach using advanced imaging and the combined experience of cardiac surgeons and interventionalists, we can accurately select the correct tools for valve repair or replacement. Although there is a deep experience with percutaneous mitral valve repair, the interventional community is still in the early phase of percutaneous mitral valve therapy. Feasibility, safety, and efficacy remain the focus, and long-term durability is not even being discussed. Upcoming research should continue to refine patient selection, device it, and at some point, a percutaneous mitral therapy may compete with surgery in terms of results and durability.

Compliance with Ethical Standards

Conflict of Interest Marvin H. Eng MD is a proctor for Edwards Lifesciences.

Dee Dee Wang MD serves as a consultant to Edwards Lifesciences, Boston Scientific, and Medtronic.

Tiberio Frisoli MD has no conflicts to report.

William W. O'Neill MD serves as a consultant to Abiomed, Boston Scientific, and Medtronic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368:1005–11.
2.• Dziadzko V, Clavel M-A, Dziadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. Lancet. 2018;391:960–9. **Seminal population study of mitral regurgitation.**
3. Monteagudo Ruiz JM, Galderisi M, Buonauro A, et al. Overview of mitral regurgitation in Europe: results from the European Registry of mitral regurgitation (EuMiClip). Eur Heart J Cardiovasc Imaging. 2018:19(5):503–7.
4. Regueiro A, Granada JF, Dagenais F, Rodés-Cabau J. Transcatheter mitral valve replacement: insights from early clinical experience and future challenges. J Am Coll Cardiol. 2017;69:2175–92.
5. Maisano F, Alfieri O, Banai S, Buchbinder M, Colombo A, Falk V, et al. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? Eur Heart J. 2015;36:1651–9.
6.• Ho SY. Anatomy of the mitral valve. Heart. 2002;88:iv5–iv10. **Fundamental characterization of mitral valve anatomy.**
7. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. I. A two-dimensional echocardiographic method and findings in normal subjects. Circulation. 1981;64:113–20.
8. Filsoufi F, Carpentier A. Principle in reconstructive surgery in degenerative mitral valve disease. Semin Thorac Cardiovasc Surg. 2007;19:103–10.
9. McCarthy KP, Ring L, Rana BS. Anatomy of the mitral valve: understanding the mitral valve complex in mitral regurgitation. Eur J Echocardiogr. 2010;11:i3–9.
10. Rusted IE, Scheifley CH, Edwards JE. Studies of the mitral valve. I. Anatomic features of the normal mitral valve and associated structures. Circulation. 1952;6:825–31.
11. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation. 2014;129:2440–92.
12. Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR Jr, Stebbins A, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT Registry report. J Am Coll Cardiol. 2017;70:2315–27.
13. Schafer U, Maisano F, Butter C, et al. Impact of preprocedural left ventricular ejection fraction on 1-year outcomes after MitraClip implantation (from the ACCESS-EU phase I, a prospective, multicenter, nonrandomized postapproval study of the MitraClip therapy in Europe). Am J Cardiol. 2016;118:873–80.
14. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J. 2016;37:703–12.
15. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011;364:1395–406.
16. Praz F, Spargias K, Chrissoheris M, Büllesfeld L, Nickenig G, Deuschl F, et al. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. Lancet. 2017;390:773–80.
17. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. J Am Coll Cardiol. 2015;66:2844–54.
18.• Thaden JJ, Malouf JF, Nkomo VT, Pislaru SV, Holmes DR Jr, Reeder GS, et al. Mitral valve anatomic predictors of hemodynamic success with transcatheter mitral valve repair. J Am Heart Assoc. 2018;7(2):e007315. **Illustration of the predictors of clinical success with edge-to-edge repair.**
19. Lesevic H, Karl M, Braun D, Barthel P, Orban M, Pache J, et al. Long-term outcomes after MitraClip implantation according to the presence or absence of EVEREST inclusion criteria. Am J Cardiol. 2017;119:1255–61.
20. Neuss M, Schau T, Isotani A, Pilz M, Schöpp M, Butter C. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. J Am Coll Cardiol Intv. 2017;10:931–9.
21. Cheng R, Dawkins S, Tat E, Makar M, Hussaini A, Makkar RR, et al. Relation of residual mitral regurgitation despite elevated mitral gradients to risk of heart failure hospitalization after MitraClip repair. Am J Cardiol. 2017;120:1595–600.
22. Geis NA, Puls M, Lubos E, Zuern CS, Franke J, Schueler R, et al. Safety and efficacy of MitraClip therapy in patients with severely impaired left ventricular ejection fraction: results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail. 2018;20:598–608.
23. D'Ascenzo F, Moretti C, Marra WG, et al. Meta-analysis of the usefulness of Mitraclip in patients with functional mitral regurgitation. Am J Cardiol. 2015;116:325–31.
24. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Eur J Heart Fail. 2012;14:931–8.
25. Lipiecki J, Siminiak T, Sievert H, Müller-Ehmsen J, Degen H, Wu JC, et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. Open Heart. 2016;3:e000411.
26.• Tops LF, Van de Veire NR, Schuijf JD, et al. Noninvasive evaluation of coronary sinus anatomy and its relation to the mitral valve annulus: implications for percutaneous mitral annuloplasty. Circulation. 2007;115:1426–32. **Manucript describing the relationship between the coronary sinus, mitral anulus, and coronary vessels relevant for coronary sinus annuloplasty devices.**
27. Kim J-H, Kocaturk O, Ozturk C, Faranesh AZ, Sonmez M, Sampath S, et al. Mitral cerclage annuloplasty, a novel transcatheter treatment for secondary mitral valve regurgitation: initial results in swine. J Am Coll Cardiol. 2009;54:638–51.
28. Nickenig G, Hammerstingl C, Schueler R, et al. Transcatheter mitral annuloplasty in chronic functional mitral regurgitation: 6-month results with the cardioband percutaneous mitral repair system. J Am Coll Cardiol Intv. 2016;9:2039–47.
29. Gammie JS, Bartus K, Gackowski A, D'Ambra MN, Szymanski P, Bilewska A, et al. Beating-heart mitral valve repair using a novel ePTFE cordal implantation device: a prospective trial. J Am Coll Cardiol. 2018;71:25–36.
30. Muller DWM, Farivar RS, Jansz P, Bae R, Walters D, Clarke A, et al. Transcatheter mitral valve replacement for patients with symptomatic mitral regurgitation: a global feasibility trial. J Am Coll Cardiol. 2017;69:381–91.

31. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609–20.
32. Blackstone EH, Suri RM, Rajeswaran J, Babaliaros V, Douglas PS, Fearon WF, et al. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral transcatheter aortic valve replacement: a placement of aortic transcatheter valves (PARTNER)-I trial substudy. Circulation. 2015;131:1989–2000.
33. Ribeiro HB, Nombela-Franco L, Munoz-Garcia AJ, et al. Predictors and impact of myocardial injury after transcatheter aortic valve replacement: a multicenter registry. J Am Coll Cardiol. 2015;66:2075–88.
34. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation. 2010;121:973–8.
35.• Wang DD, Eng MH, Greenbaum AB, et al. Validating a prediction modeling tool for left ventricular outflow tract (LVOT) obstruction after transcatheter mitral valve replacement (TMVR). Catheter Cardiovasc Interv. 2017;92(2):379–87. **Seminal paper characterizing the surface area required before left ventricular outflow obstruction occurs.**
36. Greenbaum AB, Condado JF, Eng M, et al. Long or redundant leaflet complicating transcatheter mitral valve replacement: case vignettes that advocate for removal or reduction of the anterior mitral leaflet. Catheter Cardiovasc Interv. 2017;92(3):627–32.
37. Babaliaros VC, Greenbaum AB, Khan JM, Rogers T, Wang DD, Eng MH, et al. Intentional percutaneous laceration of the anterior mitral leaflet to prevent outflow obstruction during transcatheter mitral valve replacement: first-in-human experience. JACC Cardiovasc Interv. 2017;10:798–809.
38. Guerrero M, Wang DD, Himbert D, Urena M, Pursnani A, Kaddissi G, et al. Short-term results of alcohol septal ablation as a bail-out strategy to treat severe left ventricular outflow tract obstruction after transcatheter mitral valve replacement in patients with severe mitral annular calcification. Catheter Cardiovasc Interv. 2017;90:1220–6.
39. Cheung A, Webb JG, Barbanti M, Freeman M, Binder RK, Thompson C, et al. 5-year experience with transcatheter transapical mitral valve-in-valve implantation for bioprosthetic valve dysfunction. J Am Coll Cardiol. 2013;61:1759–66.
40. Ye J, Cheung A, Yamashita M, Wood D, Peng D, Gao M, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves: an 8-year single-center experience. JACC Cardiovasc Interv. 2015;8:1735–44.
41. Whisenant B, Jones K, Miller D, Horton S, Miner E. Thrombosis following mitral and tricuspid valve-in-valve replacement. J Thorac Cardiovasc Surg. 2015;149:e26–9.
42. Eng MH, Greenbaum A, Wang DD, Wyman J, DNP, Arjomand H, et al. Thrombotic valvular dysfunction with transcatheter mitral interventions for postsurgical failures. Catheter Cardiovasc Interv. 2017;90:321–8.
43. Butnaru A, Shaheen J, Tzivoni D, Tauber R, Bitran D, Silberman S. Diagnosis and treatment of early bioprosthetic malfunction in the mitral valve position due to thrombus formation. Am J Cardiol. 2013;112:1439–44.
44. Korber MI, Silwedel J, Friedrichs K, et al. Bleeding complications after percutaneous mitral valve repair with the MitraClip. Am J Cardiol. 2018;121:94–9.
45. Ben-Avi R, Orlov B, Sternik L, Kogan A, Kuperstien R, Shalabi A, et al. Short- and long-term results after prosthetic mitral valve implantation in patients with severe mitral annulus calcification. Interact Cardiovasc Thorac Surg. 2017;24:876–81.
46. Guerrero M, Urena M, Himbert D, Wang DD, Eleid M, Kodali S, et al. 1-Year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. J Am Coll Cardiol. 2018;71:1841–53.
47. Eng MH, Wang DD. Transcatheter mitral valve therapy: defining the patient who will benefit. Curr Cardiol Rep. 2018;20:107.