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Transcatheter therapy for tricuspid regurgitation: The surgical perspective

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ABSTRACT

Tricuspid regurgitation (TR) remains a complex valve pathology affecting nearly two million people in the United States. Although it can present as a primary valve pathology, TR often presents as a late finding in patients with severe pulmonary disease or end-stage chronic heart failure. Surgical repair of isolated TR or TR from left-sided pathology has been associated with high morbidity and mortality. Furthermore, surgery for patients with TR and advanced cardiac disease has been associated with poor long-term outcomes. In recent years, transcatheter technology has emerged to target high-risk surgical patients with TR. Currently, multiple new transcatheter strategies to treat TR have shown initial benefit. However, further development of this technology is required. The aim of this perspective is to provide an overview of TR pathophysiology and to highlight the successful aspects of surgery for TR that provide insight for further translation of transcatheter strategies for patients with TR. These include replication of successful surgical techniques (ring-based annuloplasty and valve replacement) and the goal of achieving no to minimal residual TR following intervention. Earlier implementation of transcatheter valve repair to minimize TR progression and further development of transcatheter valve replacement strategies are also next steps in the translation of this technology.

Contents

Introduction

Although initially considered the "forgotten valve," there has been resurgence in interest and developmental research to treat pathologies of the tricuspid valve (TV).[1] Moderate to severe tricuspid regurgitation (TR) affects nearly two million people in the United States.[2] Despite an incidence of nearly 200,000 cases of TR per year in the U.S., only

Abbreviations: AV, Atrioventricular; HF, Heart failure; LV, Left ventricular; MR, Mitral regurgitation; NYHA, New York Heart Association; QoL, Quality of life; TA, Tricuspid annulus; TR, Tricuspid regurgitation; TTVR, Transcatheter tricuspid valve replacement; TV, Tricuspid valve.

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8000 TV operations are performed annually, leaving a large number of untreated patients.[3]

TR can be highly debilitating and has been associated with increased morbidity and mortality for patients. Left-sided heart pathologies can lead to chronic pressure overload of the right ventricle (RV) leading to progressive RV dilation, tricuspid annulus (TA) dilation, and subsequently, functional TR. After development of TR, patients can have significant clinical symptoms and decreased quality of life (QoL).[4] Decreased cardiac output from TR can even result in right-sided heart failure (HF), leading to hepatosplenomegaly, ascites, peripheral edema, and failure to thrive. Although mild TR is frequently observed in asymptomatic patients, moderate to severe TR frequently causes symptoms. Furthermore, patients with moderate to severe TR have been shown to have increased mortality, prolonged hospitalization, and higher rates of rehospitalization.[5–7]

Current first-line treatment strategies involve diuretics and HF medications, which are often ineffective. Surgical intervention, however, remains high-risk in patients with severe TR and progressive heart disease. As patients commonly develop TR after surgery for left-sided valve pathology, there is an unmet need for low-risk treatment strategies for these high-risk patients. In recent years, transcatheter strategies have emerged as a minimally invasive approach for high-risk patients with TR. As pre-clinical and clinical data supporting transcatheter strategies continues to accumulate, several barriers to successful implementation remain. The aim of this perspective article is to provide an overview of TR pathophysiology and to highlight the successful aspects of surgery for TR that inform implementation of transcatheter strategies for treating TR. These include replicating well-established, successful open surgical techniques (ring-based annuloplasty and valve replacement) through a transcatheter approach, and achieving no to minimal residual TR following intervention. Earlier implementation of transcatheter valve repair to minimize TR progression and further development of transcatheter valve replacement strategies are opportunities for improving treatment of TR with transcatheter technology.

Anatomic challenges

In order to be aware of the potential pitfalls of transcatheter therapy for TR, a thorough understanding of surgical anatomy is required. The TV apparatus, which has an area of four to six cm, consists of three leaflets of variable size, including the anterior (largest), posterior, and septal (smallest) leaflets (Fig. 1). The anterior and posterior leaflets are tethered to an anterior papillary muscle, while the posterior and septal leaflets are tethered to a posterior papillary muscle.[4] Although there is no septal papillary muscle, the interventricular septum anchors the chordae tendinae to the anterior and septal leaflets.[4] However, there are also accessory chordal attachments involving the RV free wall and moderator band.[4] Overall, these highly variable chordal attachments can serve as mediators of improper leaflet coaptation.[8]

The TA is a collagenous ring that serves as the line of TV leaflet attachment. It is often thin, difficult to identify, and has a dynamic shape and size. In physiologic conditions, the TA has a semi-lunar, non-planar, three-dimensional saddle-shape configuration.[9] The anteroseptal portion maintains the highest location in the TA, while the posteroseptal portion is the lowest. Furthermore, the TA shape is highly dynamic during each cardiac cycle, with as much as a 19% reduction in annular circumference during atrial systole.[10] When functional TR develops, there is a disruption of this non-planar TA orientation, leading to a more planar and circular shape, which results in TA dilatation. As such, annular reduction and restoration of the TA configuration is crucial to restoring anatomy for patients with TR.

There are also several important nearby structures that are potential challenges for the treatment of TR. The atrioventricular (AV) node lies near the atrial septum bordering the septal leaflet. The bundle of His, an extension of the AV node, is near the interventricular membranous septum and runs along the crest of the muscular septum. The right coronary artery also runs just anterior to the anterior leaflet annulus. For transcatheter strategies, these structures must be kept in mind, as

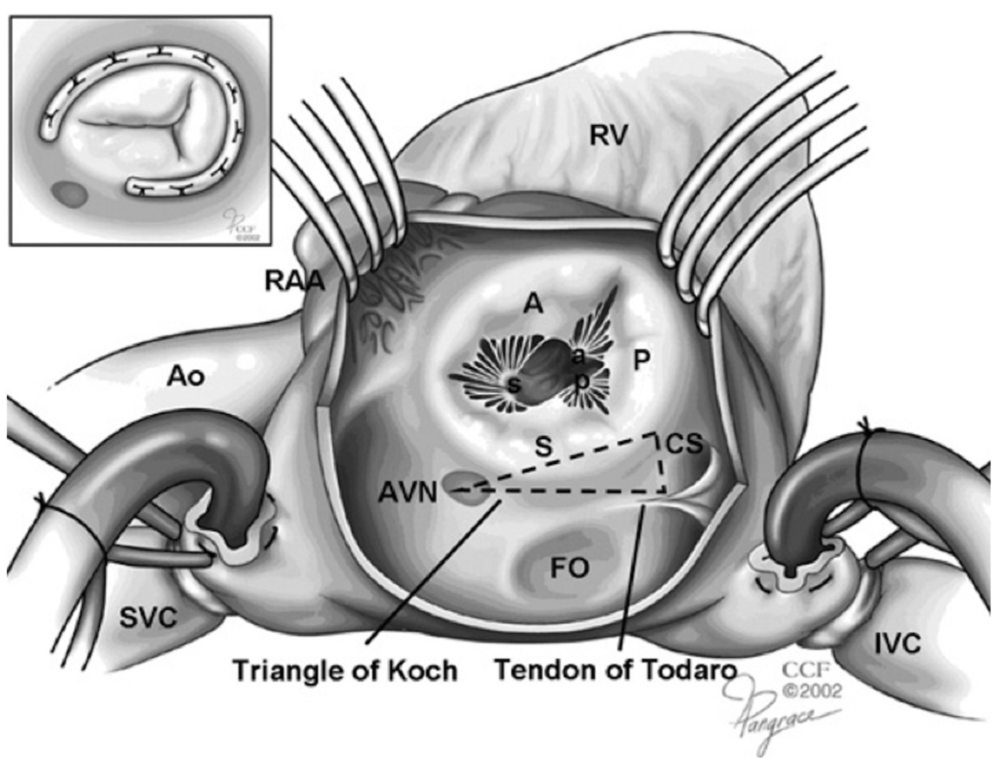

Fig. 1. Tricuspid Valve Apparatus. The tricuspid valve consists of the anterior (A), posterior (P), and septal (S) leaflets anchored by the anterior (a) and posterior (p) papillary muscles. The atrioventricular node (AVN), coronary sinus ostium (CS), and Tendon of Todaro form the Triangle of Koch. Right ventricle (RV), right atrial appendage (RAA), aorta (Ao), superior vena cava (SVC), inferior vena cava (IVC). Copyright by Cleveland Clinic Foundation (CCF), 2002.

avoiding injury is much more difficult compared to open surgical approaches.

Physiologic changes of TR

Although TR may result from primary valve pathology (infective endocarditis, leaflet prolapse, congenital, and rheumatic disease), TR is most often functional or secondary.[11] A left-side heart pathology, such as left ventricular (LV) dysfunction or atrial fibrillation, can lead to elevated pulmonary artery pressures, resulting in RV strain, TA dilation, and TR. However, TR development is also highly prevalent following repair of left-sided valve pathology. Overall, the development of functional TR can be classified into three progressive stages of disease[12]:

Stage I: Early TA Dilatation. In the first phase, the TA becomes dilated, typically secondary to RV enlargement. However, this may also be secondary to right atrial enlargement, especially in patients with atrial fibrillation. Functional TR may or may not be present as this early stage.

Stage II: Moderate TA Dilatation and Abnormal Leaflet Coaptation. As the RV becomes progressively dilated, the TA dilatation worsens. This mainly occurs with preferential dilation of the anterior and posterior leaflets. As a result, malcoaptation occurs primarily between the anteroposterior and posterolateral commissures. As such, the severity of functional TR worsens significantly.

Stage III: Severe TA Dilatation and TV Leaflet Tethering. As RV dilatation progresses, TA dilatation becomes severe, resulting in tethering of the TV leaflets. This is secondary to the attachments of the leaflets to the papillary muscles of the free wall of the RV.

Overall, these various stages of diseases provide insight into the pathophysiology of TR development. TA dilatation appears to play a central role in the development and worsening of TR. As such, it should be an early target of transcatheter strategies in the treatment of TR.

Lessons from the surgical frontline

For transcatheter therapies to be successful, it is important to be familiar with well-established open surgical techniques that have been highly effective for patients with TR. The current surgical treatment for TR without leaflet abnormalities is TV reconstruction. In the majority of patients with TR, the TV leaflets remain normal and malcoaptation occurs secondary to TA dilatation. As such, several techniques have been proposed addressing the annular or commissural anatomy, including using either suture-based or prosthetic ring-based annuloplasty.[13] Over the last decade, however, there has been much debate regarding the superior technique.

Among the suture-based techniques, the De Vega and Kay techniques are the most commonly implemented. The De Vega technique[14] involves suture annuloplasty overlying the anterior and posterior leaflets. It is fast, easy, cost-effective, and maintains the flexibility of the TA. The Kay technique,[15] also known as Kay bicuspidalization, however, involves double-pledgeted mattress sutures placed along the anteroposterior commissure to the posteroseptal commissure. Although some studies have demonstrated good short- and long-term outcomes with these techniques,[16,17] others have questioned their durability as there is a high incidence of recurrent TR, particularly in the setting of concurrent pulmonary hypertension and TA dilatation.[18]

Within the last decade, ring-based annuloplasty has emerged as a superior technique to suture-based techniques and is currently considered the gold standard of annuloplasty for patients with TR. Initial studies demonstrated superior mid-term performance and lower recurrence of moderate and severe TR.[19] Follow-up studies have confirmed these findings. Patients undergoing ring-based annuloplasty have had decreased early mortality compared to both De Vega and Kay suture annuloplasty.[20] Furthermore, ring-based annuloplasty also affords significantly decreased risk of recurrent moderate TR out to 15 years following surgery.[20] In general, rigid rings have yielded the best long-term results when compared to flexible rings and bands. Although randomized controlled trials are currently underway (ClinicalTrials.gov Identifier: NCT03144024), current findings suggest that rigid, ring-based annuloplasty techniques afford better protection against recurrent TR and improved earlier survival.[20] Regardless of TR stage, the presence of TA dilatation demonstrates irreversible progression of functional TR development. As surgical ring-based annuloplasty directly addresses TA dilation, which is a primary mediator of TR, this should be the ultimate target of correction for transcatheter-based strategies.

Other surgical valve repair techniques exist, but are used less frequently.[21] Edge-to-edge repair, initially described for treatment of mitral regurgitation (MR), can be used as an adjunctive technique to annuloplasty to treat complex lesions and severe residual TR.[22,23] In the clover technique, the midpoints of the TV leaflets are stitched together producing a triple orifice repair.[22] Small case series have demonstrated favorable results with mild or less TR at the end of the surgery, but trivial to mild TR upon two-year follow-up.[22,23] Other techniques exist including leaflet augmentation, quadrangular resection, the Hetzer technique, and combinations of multiple techniques.[21] However, these are not as well-established and are considered adjunctive to the gold standard of rigid, ring-based annuloplasty.

For patients with TV leaflets that are severely diseased and not amenable for repair, valve replacement has been highly successful and is considered the gold standard technique. This approach addresses both severe valvular disease and prevents recurrent TR with disease progression. Although mechanical valve implantation provides long-term durability, it must be weighed against the risks of aggressive anticoagulation. Biological prostheses may also be employed, however, there is risk of inevitable valve degeneration. With the advent of valve-in-valve technologies in recent years, biological prostheses can be deployed easily and repeated if needed, reducing the need for mechanical valve implantation with anticoagulation. As surgical TV replacement strategies have proven successful in select patients with leaflets not amenable to repair, we feel that transcatheter therapies should also aim to replicate this technique, in addition to rigid, ring-based annuloplasty.

Transcatheter-based therapies for TR

Patients with moderate to severe TR often have limited treatment options as surgery is often not pursued given the high risk of this patient population. There are even more risks for patients who have developed TR following left-sided valve surgery. As such, there is an unmet need for less invasive strategies for TR. In recent years, numerous transcatheter therapies have emerged to target this patient population. However, these treatments are at an early stage of implementation and have mostly been applied in compassionate use or small feasibility trials with limited clinical data. At present, there are a substantial number of anatomic strategies through which transcatheter therapies attempt to address patients with TR. While some reproduce open surgical concepts including suture and ring-based annuloplasty, many alternative strategies exist that fail to replicate surgical techniques. We choose to discuss the most popular transcatheter approaches for TR and highlight their potential benefits and weaknesses. In our view, only those transcatheter therapies that replicate the surgical gold standards of ring-based annuloplasty and TV replacement appear to have the most promising clinical outcomes.

Coaptation devices

Several transcatheter coaptation devices aim to address leaflet malcoaptation in severe TR replicating edge-to-edge repair. Two major devices exist, including the Forma Repair System (Edwards Lifesciences, Irvine, CA) and the TriClip, which is an off-label use of the MitraClip System (Abbot Vascular, Santa Clara, CA).

The Forma Repair system uses an expandable, foam-filled balloon spacer placed within the TA that is anchored to the septal portion of the RV apex (Fig. 2A). This device fills the central TA to decrease the regurgitant area, providing a new coaptation surface for leaflets. Since its introduction, the device has been applied in over 20 compassionate-use cases and an early feasibility trial of 25 patients.[24] In the short-term, patients have had decreased New York Heart Association (NYHA) scoring, improved six-minute walk testing, and improved cardiomyopathy questionnaire failure scores.[24] However, patients only experienced reduction to moderate and severe TR, including proximal isovelocity surface area (1.1 ± 0.6 to 0.6 ± 0.4 cm^2), vena cava width (12.1 ± 3.3 to 7.1 ± 2.2 mm), annular and RV base diameters (4.4 ± 0.7 to 4.5 ± 0.9 cm; 5.9 ± 0.9 to 5.5 ± 1.0 cm).[24] Although this device provides some reduction in TR, most patients continued to have severe TR following intervention, highlighting need for further improvement in this approach to address TR.

The TriClip system, initially broadly used as the MitraClip system for treatment of MR, has become a first-line approach for patients with functional TR (Fig. 2B). This is largely due to wide availability and operator familiarity. This technique involves implantation of one or more clips on the TV edges, ultimately reducing regurgitant flow. In 2017, Nickennig et al. reported the feasibility and safety of Mitraclip to treat TR in 64 patients.[25] Patients had improved exercise capacity and a reduction in diuretic dose. However, 88% of patients continued to have NYHA class II or III symptoms. Furthermore, these findings were far from surgical outcomes as 76% of patients continued to have moderate or severe TR. We recognize that technique has now changed in recent years to bicuspidalization (from multiple commissural sites) and outcomes data are lacking with this new technique. However, this approach of addressing coaptation requires further evaluation as the long-term impact of persistent moderate to severe TR following intervention remains unacceptable for non-compassionate use in patients with mild, moderate, and severe TR. The TRILUMINATE trial (ClinicalTrials.gov Identifier: NCT03227757) is currently underway and will attempt to evaluate this technology in patients with moderate to severe TR.

It is also worth highlighting that this technology has been better evaluated in severe secondary MR compared to TR. In recent years, several clinical trials evaluating transcatheter treatment for MR have emerged, but have demonstrated conflicting results. While the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated positive results,[26] the Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device In Patients with Severe Secondary Mitral Regurgitation (MITRA-FR) trial demonstrated negative results.[27] Overall, this may highlight the need for better patient selection for these techniques or that other technologies, such as transcatheter ring-based repair or valve replacement strategies, may provide better patient outcomes.

Suture-based annuloplasty therapies

The Trialign device (Mitralign, Tewksbury, MA) replicates the modified Kay bicuspidization suture annuloplasty by eliminating the posterior TV leaflet (Fig. 2C). To achieve this, pledgets are placed at the anteroposterior and posteroseptal commissures and are tightened using a plication device. In early results from the multi-center SCOUT study, 39 patients had significant reductions in TA annular diameter (3.97 ± 0.6 to 3.69 ± 0.5 cm), TV effective regurgitant orifice area (EROA) (0.92 ± 0.32 to 0.77 ± 0.43), and TV area (12.3 ± 2.4 to 10.98 ± 2.28) by 30 days.[28] Patients also reported improvement in QoL measures. Similarly, the TriCinch system (4Tech Cardio, Galway, Ireland) replicates the Kay annuloplasty technique by reducing the septerolateral diameter of the TA by tightening the anteroposterior commissure (Fig. 2D). The device involves a corkscrew anchor near the anteroposterior commissure attached to an anchor that is deployed in the subhepatic inferior vena cava. Early work has demonstrated success with a TR grade reduction from grade 4 to grade 3.[29] Despite both devices being early in clinical translation, these techniques overall fail to achieve no to minimal residual TR following intervention, which may continue to place patients at risk for significant long-term morbidity and mortality.

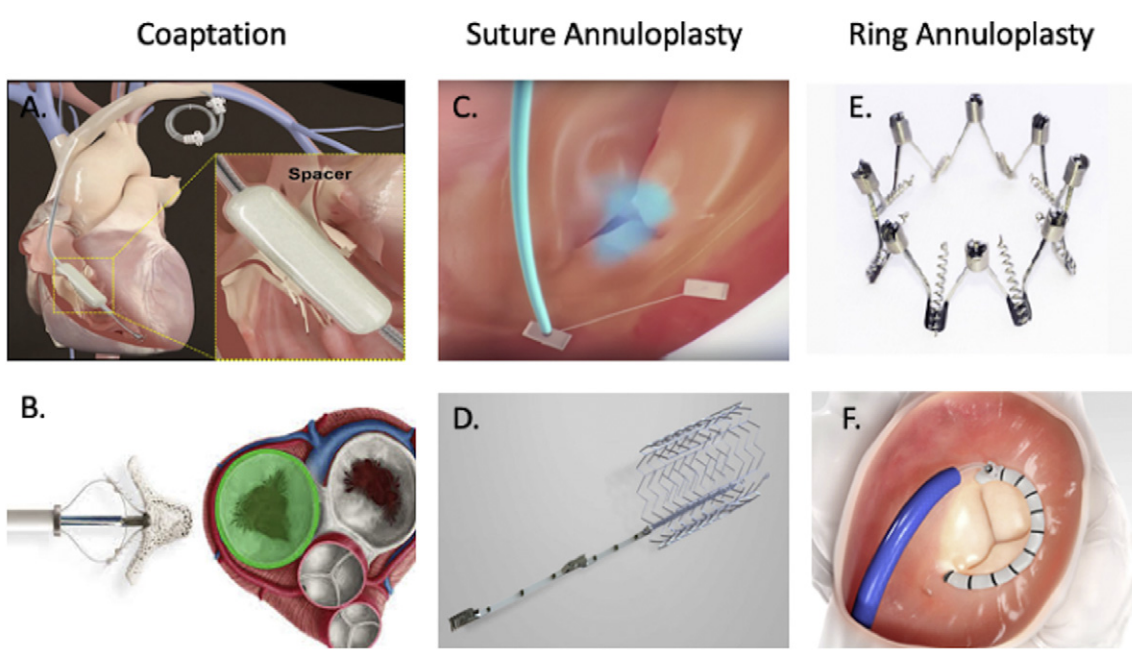

Fig. 2. Transcatheter Strategies. Several anatomic techniques replicating surgical strategies exist including coaptation, suture annuloplasty, and ring annuloplasty. The Forma System (A), TriClip System (B), TriAlign System (C), TriCinch System (D), Millipede IRIS system (E), and Cardioband System (F).

Ring-based annuloplasty techniques

In recent years, the Millipede IRIS System (Boston Scientific, Marlborough, MA) has emerged as a highly promising strategy for the treatment of TR (Fig. 2E). The system involves a completely adjustable, semi-rigid annuloplasty ring that mimics the surgical gold standard of rigid, ring-based annuloplasty. The device consists of a zig-zagged frame with anchors attaching the ring to the TA. Although it has further translation in MR, the IRIS ring has been surgically implanted using a transcatheter system in two patients with TR undergoing concurrent mitral valve repair.[10] Patients sustained a decreased TA diameter of 40% with no residual TR after 12 months. Although early in translation, initial data suggests that this may one of the first transcatheter techniques offering equivalent outcomes to surgical repair. This IRIS system has since been implemented via a transcatheter-based approach with impressive results for MR. Patients have had a reduction in baseline MR of 3–4+ to 0–1+ in all patients at 30 days with a 37% reduction in diastolic LV volumes at 30 days. Further testing is underway in both MR and TR; however, this approach is highly promising as it replicates the gold standard of surgical repair for TR—ring-based annuloplasty. Furthermore, it provides a complete ring as opposed to a partial ring, which provides stability in patients with the severest of TR. The Millipede system also requires meticulous placement as there is risk of compressing the AV node; however, this risk is minimized by not anchoring the ring in the vicinity of the AV node. The two patients who received surgical implantation using the transcatheter IRIS system are >2 years out from treatment with no evidence of recurrent TR.

The Cardioband Tricuspid Repair System (Edwards Lifesciences), which is an adjustable surgical-like Dacron band currently approved for MR, has also demonstrated promising results in TR (Fig. 2F). The device enables a partial band to be placed at the TA. The band is then cinched providing a reduction in the anteroposterior and septerolateral TA dimensions. In early studies, the first 30 patients with TR > 2 and annular diameter > 40 mm had an average of a 17% reduction in septerolateral diameter along with significant reductions in vena contracta (31%) and regurgitant orifice area (50%).[30] Initial results appear promising and additional patients are currently being recruited. However, further advancement of this technology is required as cinching may be extremely difficult and ineffective in patients with severe TA dilatation.

Valve and valve-in-valve replacement strategies

For patients with severe leaflet tethering and malcoapation, transcatheter TV replacement (TTVR) has emerged as a potential option in recent years (Fig. 3). The NaviGate bioprosthesis (NaviGate Cardiac Structures, Lake Forest, CA) is currently the only device available to achieve human orthotopic TTVR (Fig. 3A). The NaviGate valve involves a self-expanding atrioventricular valved stent with three xenogenic pericardial leaflets. Because of the large device and delivery system size, it is introduced via 42-F introducer through the transjugular vein or a transatrial approach (right anterolateral mini-thoracotomy). Since implementation in 11 humans, the initial results appear promising.[30] Following deployment, all patients had either no, trivial, or mild TR with >60% reductions in central venous pressure. Furthermore, 91% successful device implantation was achieved. Further modifications for device improvement are underway, but the initial proof-of-concept results appear promising and similar to open surgical outcomes.

The concept of valve-in-valve transcatheter replacement has also emerged in recent years. For high-risk patients with a failed bioprosthesis, this approach offers a lower-risk and less invasive alternative to re-do surgical valve replacement. Currently, there are two available transcatheter systems (Fig. 3B and C). The Medtronic Melody valve system (Medtronic Inc., Minneapolis, MN) involves a balloon-expandable prosthesis with a bovine jugular vein valve and a platinum-iridium frame (Fig. 3B), while the Edwards Sapien valve (Edwards Lifesciences, Irvine, CA), which is a bovine pericardial valve on a chromium-cobalt frame, is also available (Fig. 3C). In the largest study (156 patients) evaluating valve-in-valve replacement after failed bioprosthesis placement, initial results have been favorable.[31] Patients had significantly decreased right atrial to ventricular inflow and TR was abolished. Furthermore, 77% of patients remained in NYHA class I or II following intervention, compared to class III or IV pre-intervention. Further studies with larger patient cohorts and longer-term follow up are required, but these initial results are promising and replicate a well-established surgical technique for diseased TV leaflets.

Current clinical challenges and future application

Although transcatheter therapies have demonstrated promise in recent years, many challenges still exist. First, there remains a lack of consistency in efficacy among transcatheter approaches for TR, making it difficult to compare treatment strategies. Some studies have focused on objective parameters including alterations in TR grade, TA dilatation, and TV effective regurgitation orifice area, while others have focused on QoL outcomes including diuretic down-titration, specific QoL measures, and functional capacity. However, these have varied highly among studies and require standardization to make definitive conclusions.

To further advance the current technology and to provide the best possible clinical outcomes, there are several areas that the current transcatheter industry should aim to improve. As stated previously, transcatheter therapies for TR have been primarily utilized in compassionate cases and with limited numbers of high-risk patients in early trials. These patients have predominantly had severe, massive, or torrential TR. Although these patients had TR grade reduction after transcatheter therapies, most of these patients continued to have moderate to severe TR, which is associated with significant morbidity and mortality. Although residual moderate and severe TR may be acceptable for compassionate use or patients with scant therapeutic options, these results are still clearly inferior to surgical repair. As surgery can achieve

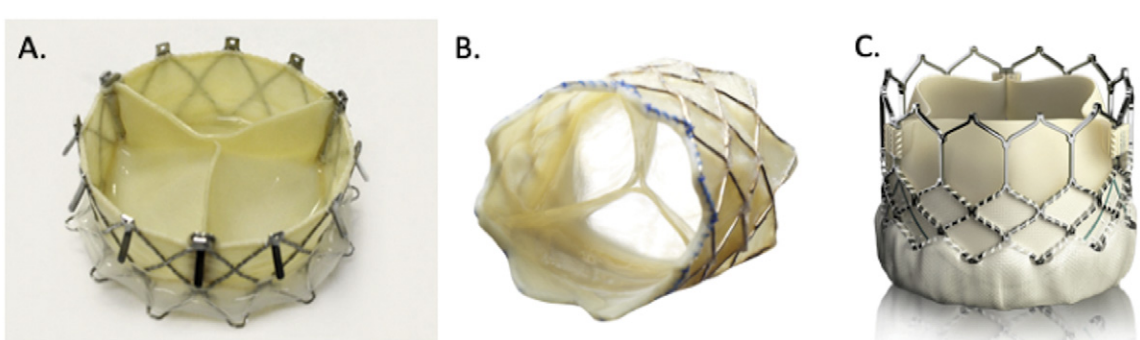

Fig. 3. Transcatheter Valve Strategies. Complete valve and valve-in-valve replacement strategies exist. The included the NaviGate System (A), Medtronic Melody valve (B), and Edwards Sapien valve (C).

no to minimal residual TR, which decreases the long-term morbidity and mortality of TR, transcatheter therapies should aim to replicate these results. Ultimately, this may require new technologies or a combination of various strategies. However, in our view, replication of surgical techniques to address TA dilatation and severely diseased leaflets through rigid, ring-based annuloplasty and TV replacement will provide optimal outcomes.

A next step in the translation of transcatheter ring-based annuloplasty strategies involves targeting patients earlier in the progression of TR. Most of the current transcatheter technology has been evaluated late in the progression of TR. As such, it fails to target the early window leading to the irreversible pathologic changes of TR. This includes TA dilatation and RV alterations. As ring-based annuloplasty is often administered for early TA dilation treatment with or without TR during left-sided valve surgery, we feel that transcatheter therapies should attempt to mimic this implementation strategy. Furthermore, as the RV and TA have been shown to exhibit cardioplasticity following TR regression,[32] we feel that a more aggressive interventional approach should be implemented. As early feasibility and safety have now been demonstrated, the next step would be applying this technology safely in patients with mild to moderate TR. This may ultimately allow for remodeling of RV alterations, including a reduction of TA diameter and an increase in TV coverage. Further studies, however, are required to determine which patients will benefit from early intervention.

We would also like to highlight that new TR grading schemes have been proposed in recent years.[33] These include the traditional grading scale including mild, moderate, and severe TR, but also the addition of massive and torrential grades of TR.[33] Although such scales may further classify patients with the severest of TR, we feel that these new grades of TR should not be the benchmarks by which we evaluate the treatment of TR. As moderate to severe TR are already well known to be associated with significant morbidity and mortality,[5,7] targeting no to minimal residual TR, which replicates what surgical TV repair or replacement can achieve, should be our standard of care for patients with TR.

Lastly, high-risk patients with severe disease with TA dilatation, malcoaptation, and unrepairable TV leaflets also represent a targetable population for TVVR. As surgical valve replacement has proven highly successful in select patient populations, the transcatheter industry should also focus on advancing this technology. Initial TVVR and valve-in-valve technologies have proven promising. With further advancement of technology and additional study, we anticipate TTVR to be a high impact strategy for select high-risk patients with TR with diseased leaflets. This ultimately may help to avoid a high-risk operation in patients with highly co-morbid conditions.

Conclusions

In conclusion, transcatheter therapies remain a promising avenue for patients who are high risk for surgical treatment of TR. In recent years, numerous transcatheter techniques have emerged. In our view, we anticipate only those techniques that replicate the surgical gold standards of rigid, ring-based annuloplasty and TV replacement will be the most successful. Overall, further work remains in the translation of transcatheter therapies for TR, which includes achieving no to minimal residual TR after intervention. Earlier implementation of transcatheter TV repair to minimize TR progression and further development of TTVR strategies are also next steps in the translation of this technology.

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None.

Declaration of competing interest

Dr. Steven F. Bolling is a consultant to Boston Scientific (Marlborough, MA). No other conflicts of interest.

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