Interventional Cardiology Perspective of Functional Tricuspid Regurgitation

Shikhar Agarwal, MD, MPH; E. Murat Tuzcu, MD; E. Rene Rodriguez, MD; Carmela D. Tan, MD; L. Leonardo Rodriguez, MD; Samir R. Kapadia, MD

A vast unmet need exists for tricuspid valve (TV) repair for functional tricuspid regurgitation (FTR) among patients undergoing left heart valve surgery. The FTR is a dynamic entity that is governed by several pathophysiologic mechanisms like TV annular dilatation, annular shape, pulmonary hypertension, left or right ventricle dysfunction, right ventricle geometry, and leaflet tethering. Treatment options for FTR are primarily surgical. No clear medical management exists for treatment of FTR. Several studies have demonstrated improvement in functional status along with tricuspid regurgitation grades among individuals undergoing concomitant TV repair as compared with those undergoing only left heart valve surgery, although data on mortality benefits are equivocal. Percutaneous TV technology may be initially useful for patients with FTR who are at high risk for open-heart surgery. Once the other percutaneous technologies for mitral, aortic, or pulmonary valve become widely available, the need for percutaneous TV procedures will be even more apparent. Initial data from animal studies have shown encouraging results. A concurrent effort is being invested to develop effective mechanistic models, right stent materials, superior valve devices along with a precise technology for valve deployment.

The current prevalence of moderate-to-severe tricuspid regurgitation (TR) is estimated to be 1.6 million in the United States.1 Of these, only ∼8000 patients undergo tricuspid valve (TV) surgeries annually, most of them in conjunction with left heart valve surgeries (LHVSs).1 This has resulted in a vast unmet need of recognizing and effectively treating TR in adult populations. With the decline of rheumatic heart disease, a large proportion of the TR encountered is functional rather than organic. Functional TR (FTR) refers to the TR secondary to the left heart pathology or right heart pathology in the face of a normal TV leaflet morphology.

Historical Perspectives

The methods of detecting TR have evolved considerably over the years. The initial methods included intraoperative digital exploration with qualitative right atrium and right ventricle (RV) assessment. In the 1980s, right heart angiography began to be used for the detection of TR. Concomitantly, advances in the echocardiographic technology prompted the use of 2D surface echocardiography to be used in preoperative characterization of TR. Currently, 2D echocardiography in conjunction with Doppler color flow mapping forms the mainstay of TR detection and characterization. Methods of TR detection are presented in Table 1, Figures 1 through 3, and movie clips 1 and 2.

Early in 1965, it was reported that successful mitral valve replacement (MVR) in patients with pulmonary hypertension led to a prompt reduction in pulmonary artery pressures.9 In serial studies, however, it was discovered that this reduction might be “gradual” rather than a “prompt” one, occurring over a period of months. Subsequently, Cohen et al10 reported that the changes in pulmonary hemodynamics after MVR might actually be insignificant and unpredictable.

TR is a frequent problem among patients with valvular disease. In a large retrospective cohort of 5223 patients undergoing echocardiography, Nath et al11 reported that 819 patients (15.6%) demonstrated evidence of moderate-to-severe TR. Dreyfus et al12 observed that up to 48% of the patients with chronic severe mitral regurgitation undergoing MV repair had tricuspid annular diameter greater than twice the normal size (>70 mm) regardless of the TR grade. Despite the high prevalence of FTR among patients with left heart valve pathologies and a direct implication of FTR correction on long-term outcomes, the proportion of patients undergoing TV repair remains extremely variable.

Anatomy of the TV

TV Orifice and Annulus

In anatomic position, the TV lies at an angle of 45 degrees with the sagittal plane with an inclination such that it faces somewhat inferiorly and anterolaterally to the left side. The normal TV annulus is an elliptical, nonplanar structure with a distinct bimodal or saddle-shaped pattern having 2 high points (oriented toward the right atrium) and 2 inferior points (oriented toward the RV).13 The nonplanar and noncircular...
The “fibrous skeleton of the heart” provides a stable but deformable platform for attachment of the fibrous core of the TV. Two pairs of collagenous prongs (fila cornaria) extend from the central fibrous body toward the left (forming the mitral annulus) and the right (forming the tricuspid annulus). Although the fila are more continuous near their origin, they vary greatly at peripheral points. At several peripheral sites, only fibroadipose tissue separates the right atrium and RV. Because of a lower proportion fibrous tissue and a comparatively larger size, the TV annulus is considered less robust than the MV annulus. Unlike MV, the TV annulus does not contract. Systolic dysfunction of the perianular myocardium may impact the TV annulus, resulting in TV dysfunction.

**Leaflets and Commissures**
The TV consists of 3 leaflets of unequal sizes: anterosuperior, posterior, and septal leaflets. The largest leaflet, the anterosuperior leaflet, hangs like a curtain between the inlet and outlet part of RV. It spans the aortic valve groove extending from the posterolateral aspect of the supraventricular crest (anteroinferior commissure) along its septal limb to the membranous septum, terminating at the anterosuperior commissure. The attachment of the septal leaflet extends from the inferoseptal commissure on the posterior ventricular wall.
across the muscular septum and then spans across the membranous septum to terminate at the anteroseptal commissure. The septal cusp defines 1 of the borders of the Triangle of Koch, the apex of which marks the location of the aortic valve node. The posterior leaflet is less constant than the other 2 and is completely mural in its attachment, extending from the inferoseptal commissure to the anteroinferior commissure (Figure 5).

Papillary Muscles
The leaflets are supported by papillary muscles of uneven sizes. The anterior papillary muscle (Figure 4) is the largest and arises from the anterolateral ventricular wall below the anteroinferior commissure. The medial papillary muscle is small yet typical and arises from the posterior limb of septomarginal trabecula. The bifid or trifid inferior papillary muscle is often inconstant and arises from the myocardium below the inferoseptal commissure. In addition, there is often presence of several smaller, highly variable muscles attaching the cuspal margins to the right ventricular wall. All papillary muscles send chordae to tether the respective valve leaflets. One of the characteristic differences between the RV and LV is the presence of chordae in the RV extending from the septal leaflet to the ventricular septum; such septal insertions are conspicuously absent in the LV.

Pathophysiology
TV closure is a dynamic and complex function that requires the coordinated function of valve leaflets, chordae, papillary muscles, TV annulus, and perianular myocardium along with optimal functioning of the RV. Several factors have been implicated in the development and progression of TR (Table 2).

Treatment
Several surgical options exist for treatment of FTR with normal leaflets and chordal structures. Techniques for correction of mild to moderate TR include plication of the posterior leaflet’s annulus (bicuspidization) and partial purse-string reduction of the anterior and posterior leaflet annulus (De Vega style techniques). A significant degree of FTR may require correction using rigid or flexible rings or bands placed to reduce the annular size and achieve leaflet coaptation. The majority of current surgical techniques center around reduction of a large TV annular size in correction of FTR. However, this fails to adequately address the important role of persistent leaflet tethering in the genesis of FTR.

TV replacement is mostly reserved for advanced disease arising due to structural abnormality of valve leaflets. It has been reported that TV replacement carries a much higher risk of mortality as compared with TV annuloplasty (TVA) for correction of TV anomalies. Medical treatment for FTR focuses on improving the underlying cause, whenever possible, and to mitigate its impact on the body. Different treatments strategies including conservative management can be studied in a systematic manner using end points of efficacy of TR reduction, mortality, functional status, and recurrence of TR.
Reduction in TR Grade
Several studies have reported the persistence of TR in patients undergoing LHVS alone without concomitant TV procedure. Tager et al reported that in their experience, the TV repair led to resolution of TR in 85% of patients with preoperative TR, as compared with no resolution among patients who were conservatively managed. Duran et al reported that postoperative TR was detectable in 18% of patients undergoing TV repair with LHVS compared with 53% of patients in whom TR was “ignored.” Dreyfus et al have reported that the TR grade increased by 1.4 among patients undergoing TVA with MVR, as compared with a fall of 0.5 among patients undergoing MVR alone, with a P value of 0.001. Sagie et al reported that the progress of TR (defined as increase in TR grade by at least 2 grades) was encountered in 30% of individuals undergoing LHVS alone, which was significantly higher than the 12.9% among the LHVS done in conjunction with TVA. Interestingly, the preoperative prevalence of moderate-to-severe TR among patients undergoing LHVS with TVA was 81% as compared with 0 patients with moderate-to-severe TR among patients undergoing LHVS alone. Czer et al reported that TVA provided significant (≥2+) reduction in regurgitation severity in 94%, as compared with 14% among patients undergoing MVR alone without concomitant TV procedure. Five-year follow-up from another comparative study of patients with LHVS with TVA versus LHVS alone found that concomitant TVA may cause mild TV stenosis but produces sustained preventive effects against TR. The TR jet area on long-term follow-up was found to be 5.1 cm² among the conservatively managed group as compared with 2.0 cm² among the TVA group even though TR was significantly milder preoperatively in the former group.

Mortality and Functional Status
Concomitant correction of TR with LHVS yielded in-hospital mortality of 8.9% and a 10-year survival of 78±3%. Even in cases of triple valve surgery, 1-year survival rates of 80±7%, 5-year survival rate of 75±8%, and 10-year survival rates of 41±15% have been reported. Improvement in surgical techniques reduced operative mortality for TV interventions with LHVS considerably. In a large follow-up study (1974–2003), overall 30-day mortality rates were 18.8% for the entire duration and 11.1% for a more recent period of 2000–2003.

In the experience of Dreyfus et al, where patients undergoing MVR had a thorough evaluation of the TV, TVA was performed if TV annular diameter was found to be twice the normal size (≥70 mm) regardless of the TR grade. No significant difference in short- or long-term mortality rates was observed. However, significant differences were observed in the postoperative symptomatic status of these patients. On long-term follow-up, 14.1% of the patients undergoing MVR alone had New York Heart Association class 3 to 4 symptoms as compared with none of the patients undergoing TVA with MVR remaining in New York Heart Association class 3 to 4. Another surgical group also reported that surgical correction of TR results in better functional outcome but does not affect early and late survival.

TR on Follow-Up
As mentioned earlier, residual TR is not an uncommon phenomenon after TV surgery. It is even more frequent among patients in whom the TR is “ignored” at the time of LHVS. Among the patients undergoing LHVS with TVA, 22.4% of cases have been reported to have moderate-to-severe residual TR in the immediate postoperative period. On long-term follow-up, the prevalence of residual TR may increase to as high as 31%. Czer et al have clearly indicated that residual TR detected in the immediate postoperative period either persists or deteriorates over long-term follow-up but rarely improves. A high proportion of individuals with residual TR may be in advanced stages of heart failure on long-term follow-up. McCarthy et al reported that up to 24% of the patients undergoing TV procedures were in New York Heart Association class 3 to 4 after 4 years of follow-up. Despite the high rate of heart failure among these
individuals, the rate of reoperation was merely 2.9% at 10 years, primarily because of avoidance of repeat surgeries in these patients with poor midterm survival.\textsuperscript{33} In addition, late TR occurring post-MVR requiring reoperation for correction of significant TR has an extremely high mortality rates and hence accurate detection and correction of TR at the time of initial surgery is the most effective means of preventing the occurrence of FTR.\textsuperscript{32}

\textbf{Lessons Learned From Percutaneous Mitral Valvuloplasty}

Percutaneous mitral valvuloplasty (PMV) for mitral stenosis presents a unique model to assess the impact of correction of left-sided valvular disease on progression of TR. The persistence of FTR after PMV contributes to increased morbidity and mortality despite adequate percutaneous MV intervention. Song et al\textsuperscript{34} compared the outcome of patients with mitral stenosis along with severe TR undergoing PMV to those undergoing MVR with TVA. Although significant improvement in the TR grade was observed among the latter group, no significant differences in the estimated long-term actuarial survival rates could be discerned. In Sagie’s experience,\textsuperscript{35,36} no correlation existed between the success of the procedure and resolution of the TR.\textsuperscript{36} One of the major reasons for this failure could be the lack of significant reduction in TV annular diameter due to long standing TV disease leading to irreversible changes in the TV annulus.\textsuperscript{37} This implies that to ascertain success in treatment of FTR, the TV requires intervention.

\textbf{Percutaneous TV Technology}

\textbf{Need for a Percutaneous Approach}

There is an unmet need for TV correction among patients undergoing surgery for other valvular abnormalities. There has been considerable development in percutaneous technologies for the MV, and a significant proportion of patients with MV abnormalities have concurrent TV abnormalities that need to be corrected. It is noteworthy that a high proportion of patients with mitral regurgitation and coexisting TR have poor functional status that increases their operative risk, sometimes to unacceptably high levels. Percutaneous procedures may be an attractive alternative for patients deemed to be high-risk surgical candidates. As mentioned earlier, PMV may not relieve FTR, and uncorrected TR typically worsens over time leading to poor symptomatic relief. In addition, severe TR is a relative contraindication for PMV because the outcomes of these patients are not optimal.\textsuperscript{38} Further, late...
operation or reoperation for correction of significant FTR after a prior MV procedure is associated with a high morbidity and mortality; hence, availability of a percutaneous treatment option would allow patients to have both procedures in a minimally invasive fashion possibly leading to more favorable outcomes.

**Percutaneous TV Repair and Replacement Technologies**

It remains to be seen whether percutaneous repair or replacement of the TV becomes a reality (Figure 8). Edge-to-edge repair, coronary sinus-related approaches, and ventricular remodeling concepts that are available for mitral valve repair are unlikely to work in the TV because of obvious anatomic differences. However, there are several concepts that were constructed for the treatment of mitral regurgitation, which might be applicable to TR correction as well (Figure 8). These include direct annular plication (CORDIS), the application of radiofrequency (Quantumcor), and the regurgitant orifice spacer/occluder concept. The direct annular plication is achieved by placing the clips on the annulus for plication. With the Quantumcor device, radiofrequency is applied to the annulus and induces scarring, resulting in shrinking of the annulus. The spacer/occluder technology places a device in the valve orifice over which the leaflets coapt and prevent regurgitation. GDSAccucinch is another technology that may be harvested for TV. This involves placement of anchors at select sites around the MV annulus, followed by increasing traction on the cable to reduce interanchoring distance, thereby reducing the MV annular size. Although conceptually exciting, there is still no data from animal experiments in which these technologies have been used.

Boujemline et al published one of the first studies with percutaneous TV implantation in healthy ewes. The authors used a percutaneously inserted valved stent with a nitinol cylinder separating 2 large disks with sealing achieved by a polytetrafluoroethylene membrane. In their experience, 7 of the 8 devices were successfully deployed in the desired location; 1 stent was caught up in tricuspid chordae leading to incorrect deployment; and severe paravalvular leak with instantaneous death. Among the 4 animals euthanized after 1-month postimplantation, 1 demonstrated a significant paravalvular leak. There was a significant pericardial effusion, and the polytetrafluoroethylene membrane was found to be torn beside a weld fracture. Zegdi et al report that their experience in a sheep model with a valve stent device consisting of a porcine stentless valve mounted in a 30-mm nitinol stent device. The stent consisted of 2 sutures encircling the stent at either end whose traction through a proximal handle could affect the deployed versus compressed state of the stent. This mechanism allowed precise control, and if needed, it could reverse the deployment of the valved stent.

The other proposed approach for percutaneous TV repair is the implantation of separate valves in the superior vena cava and inferior vena cava (IVC) to prevent damage to the liver and other organs due to high right-sided pressures. Percutaneous IVC valve implantation was carried out at our institution for correction of severe TR causing severe liver congestion and ascites in a high-risk patient with radiation heart disease. Despite the correction of only IVC backflow,
Figure 8. Concepts for percutaneous correction of FTR. A, Dissected heart with valved stent devices in the superior and inferior vena cava (black arrows); the spacer/occluder (white arrow) extends from the right ventricular apex to the tricuspid annular plane to facilitate an optimal coaptation of the valve leaflets. B, Appearance of the TV after millipede annuloplasty. C, Valve annulus after plication annuloplasty. D, Valved stent device deployed in the tricuspid position.

Challenges for Percutaneous TV Replacement

The TV annulus is typically twice the normal size ie, >70 mm of diameter in patients with significant FTR. It is indeed challenging to design an expandable valve of 70 mm that could be easily deployed through the femoral vein using standard sheaths and delivery catheters. Once deployed, it is necessary that the valve be securely anchored into its location to prevent paravalvular leaks, and more importantly, embolization. Trapping of the device in the chordae may be another issue. Exuberant tissue overgrowth along with nodular calcifications has been noted in the TV area compared with the MV area. This has been attributed to lower blood pressure and velocity that favor thrombi deposits in the biological valve implanted in the tricuspid position. Other challenges of percutaneous valves including stent fracture, inaccurate imaging and positioning, and paravalvular leak are relevant in percutaneous TV implantation. Access would be an important consideration due to angulation of the annulus in relation to the superior vena cava and IVC. RV access may be considered but is less robust than the LV apical approach for aortic valve due to the thin wall of the ventricle and multiple chordae.

The durability of stent material is a major consideration owing to the large size and motion of the annulus. Although balloon-expandable frames remain as options, self-expanding stents with some anchoring mechanism are preferable due to anatomic considerations. The durability of the valve is another concern due to lower pressure and a slower flow circuit. Rapid advancements in tissue valve engineering may help to solve some of these issues.

Conclusion

A vast unmet need of TV repair for FTR exists in patients undergoing LHVS. FTR is a dynamic entity that is governed by several factors including TV annular dilatation, TV annular shape, pulmonary hypertension, LV/RV dysfunction, RV geometry, and leaflet tethering. Several studies demonstrate improvement in functional status along with TR grades among individuals undergoing concomitant TV repair, in comparison with those undergoing LHVS alone, although data on mortality benefits are equivocal.

Percutaneous TV technology may be useful for patients with FTR who are at high risk for open-heart surgery. Data from initial animal studies about the feasibility of implantation and efficacy of the percutaneous TV are encouraging. Once the other percutaneous technologies for mitral, aortic, or pulmonary valve become widely available, the need for percutaneous TV procedures will be even more apparent.

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Disclosures

None.

References

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In the article by Agarwal et al, “Interventional Cardiology Perspective of Functional Tricuspid Regurgitation,” which appeared in the December 2009 issue of the journal (Circ Cardiovasc Interv. 2009;2:565–573), an error in the author listing occurred:

Carmela D. Tan, MD should be listed as an author.

Shikhar Agarwal, MD, MPH; E. Murat Tuzcu, MD; E. Rene Rodriguez, MD; Carmela D. Tan, MD; L. Leonordo Rodriguez, MD; Samir R. Kapadia, MD

Dr Tan is from Cleveland Clinic, Cleveland, OH.

These errors have been corrected in the current online version of the article (http://circinterventions.ahajournals.org/cgi/content/full/2/6/565). The authors regret the error.

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SUPPLEMENTAL MATERIAL

Movie Clip Descriptions

These video clips represent real-time 3 dimensional echocardiograms of the tricuspid valve. After obtaining the reference apical 4-chamber and 2-chamber views, full-volume datasets of tricuspid valve are visualized. As shown in movie 1, four conical subvolumes are first obtained. After the acquisition of subvolumes, these are automatically integrated to create a pyramidal volumetric representation of the tricuspid valve (movie 2). All three leaflets of the valve are clearly visualized in these 3-D images, as seen from the right ventricle. This technique is invaluable in assessment of functional tricuspid regurgitation as well as structural valvular pathology.