Morphologic Types of Tricuspid Regurgitation
Characteristics and Prognostic Implications

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ABSTRACT

Tricuspid regurgitation (TR) is classified according to different morphologic types based on the underlying mechanisms: primary, secondary, and isolated TR. Primary TR is caused by an anatomical abnormality of the tricuspid valve apparatus. Secondary TR is caused by dilation of the tricuspid valve annulus, related to right ventricular (RV), or right atrial remodeling and increased RV pressures (often secondary to left-sided heart disease). Isolated TR can exist in patients without increased RV pressures and is frequently associated with atrial fibrillation. Two-dimensional echocardiography plays a pivotal role in the assessment of the etiology and severity of TR. Views from 3-dimensional techniques have significantly increased the understanding of the pathophysiology of each morphologic type of TR (leaflet damage, annular dilation, and distinct patterns of right-heart remodeling). The following review will describe the etiology, anatomical and functional characteristics, and outcomes of each morphologic type of TR, and furthermore addresses challenging pitfalls in the referral for tricuspid valve intervention. (J Am Coll Cardiol Img 2019;12:491–9)

During the last 2 decades, insights into the natural history and pathophysiology of tricuspid regurgitation (TR) have shifted the treatment of TR from a conservative approach, to an approach of intervention and potential prevention. Advances in echocardiographic techniques and the development of 3-dimensional (3D) imaging modalities have further allowed more accurate assessment of tricuspid valve (TV) morphology, mechanisms of TR, severity of TR, and more detailed evaluation of the extent of right-heart remodeling, all potentially contributing to TR progression. Different morphologic types of TR can be distinguished, depending on the presence of a primary abnormality of the TV apparatus (primary TR), dilation of the TV annulus, leaflet tethering, and right ventricular (RV) remodeling (due to left-sided heart disease and pulmonary hypertension) (secondary TR) or atrial fibrillation (AF) and right atrial (RA) remodeling (isolated TR) (Central Illustration). Along with growing insights into the deleterious outcomes of untreated TR and high mortality risk associated with surgical intervention, novel transcatheter devices have been developed. This review will describe the different
TR is a relatively common valvular heart disease which is classified based on the underlying mechanism as primary or secondary. The estimated frequency of primary TR is 8% to 10%, less frequent than secondary TR which accounts for the most frequent mechanism of TR.

Primary TR is caused by an abnormality of any of the components of the TV apparatus (tricuspid leaflets, chordae, papillary muscles, or annulus), due to congenital or acquired causes. The most common congenital abnormality of the TV is Ebstein’s disease characterized by an apical displacement of the leaflets which arise directly from the wall of the RV without identifiable chordae (1). Acquired causes of primary TR include tumors (such as carcinoma and myxoma), iatrogenic injury (such as RV endomyocardial biopsy, transvenous pacing, or defibrillator leads), drug-induced leaflet damage (such as anorectic drugs, dopamine agonists, and ergot alkaloids) (2), systemic diseases (such as lupus erythematosus and sarcoidosis), radiation, rheumatic disease, endocarditis, and trauma (3). Among acquired causes of TR, transvenous pacemaker or defibrillator lead-induced TR is one of the most frequent etiologies. With aging of the global population and an increasing number of patients with pacemaker devices, the prevalence of lead-induced TR may increase considerably. Among patients without TR before pacemaker implantation, up to 38% may develop significant TR over the following 1 to 1.5 years after lead insertion (Figure 1) (4).

Secondary TR is frequently caused by RV dilation and dysfunction, leading to leaflet tethering, tricuspid annulus dilation, and malcoaptation (5). The most frequent causes of secondary TR include co-existing left-sided valvular and myocardial disease associated with increased left atrial pressures, pulmonary hypertension, and increased RV afterload. Thirty percent to 50% of patients with severe mitral regurgitation (6) and more than 25% of patients with severe aortic stenosis (7) show significant (moderate and severe) TR. Furthermore, after surgical or transcatheter treatment of mitral regurgitation (8-13) or aortic stenosis (14-18), progression or late onset of TR can frequently occur. Similarly, in patients with reduced left ventricular (LV) ejection fraction presenting with acute (19) or chronic (20-22) heart failure (HF), significant TR is commonly observed which can progress further despite optimal medical therapy and cardiac resynchronization therapy (Figure 1) (23).

Pulmonary hypertension, arising from other causes than left-sided heart disease, includes primary pulmonary hypertension, pulmonary embolism, and chronic pulmonary disease. These etiologies can cause TR due to increased RV afterload, RV dilation, and dysfunction. Furthermore, in the absence of pulmonary hypertension, diseases directly affecting the RV function such as ischemia in inferior myocardial infarction (24,25) or arrhythmogenic RV dysplasia/cardiomyopathy (26) can lead to TR through apical displacement of the papillary muscles and increased tethering of the TV leaflets.

Finally, other than primary or secondary TR, isolated TR is a morphologic type of TR which is increasingly recognized as a separate entity. In the absence of concomitant pulmonary hypertension or co-existing left-sided heart disease, isolated TR is mainly present in elderly patients with a high prevalence of AF causing RA dilation, TV annulus dilation, and TV leaflets malcoaptation (Figure 1) (27-29).

HOW TO ASSESS THE ANATOMICAL AND FUNCTIONAL CHARACTERISTICS OF VARIOUS TYPES OF TR

Table 1 summarizes the different echocardiographic characteristics of primary, secondary, and isolated TR. In primary TR, echocardiographic assessment of individual leaflet pathology by 2-dimensional (2D) echocardiography is particularly challenging because of anatomic variability in size and number of leaflets and only 2 TV leaflets can be visualized simultaneously on routine echocardiographic views. 3D echocardiographic imaging permits more accurate individual leaflet identification by providing the “en face” visualization of the TV, further improving assessment of leaflet morphology and mobility and involvement of the subvalvular apparatus (30,31).

Whereas myxomatous valve disease is characterized by the presence of redundant tissue with excess leaflet mobility (32), thickened leaflets with a restrictive motion can be caused by carcinoid syndrome (33) or less frequently rheumatic involvement. Lead-induced TR can be caused by impingement of the tricuspid leaflet by the lead itself, leaflet perforation, laceration or avulsion, and transection of papillary muscles or chordae tendineae (34,35). In TR after pacemaker/defibrillator-lead implantation, diagnosing the cause of TR remains challenging.
because the differentiation between an anatomical defect (primary TR) and progressive RV and tricuspid annulus dilation secondary to the existent left-sided myocardial disease (secondary TR) is difficult (36).

However, 3D echocardiography may clarify the exact mechanism of lead-related TR by identifying the lead position, route, and specific leaflet impingement (35,37).

In secondary TR, progressive tricuspid annular dilation is one of the main mechanisms (9). Several 3D echocardiographic studies have compared tricuspid annular dimensions and geometry between healthy subjects and patients with secondary TR (38–40). A nonplanar, saddle-shaped tricuspid annulus was found in healthy subjects (38) with the high points located anteroposteriorly, and the low points located mediolaterally (39). In patients with secondary TR, the annulus was more planar, circular, and dilated in the septal to lateral direction, in the direction of the RV free wall (38–40). A similar pattern of tricuspid annular remodeling in secondary TR has been shown by multidetector row computed tomography studies (41,42), and cardiac magnetic resonance imaging (43). Furthermore, RV dilation and remodeling constitute a distinct mechanism associated with the development of secondary TR. By 2D echocardiography, the presence of significant secondary TR was associated with a larger RV eccentricity index, larger tricuspid annulus and end-systolic tethering area (44). Similarly, multidetector row computed tomography studies showed a larger tricuspid annulus, enlarged RV dimensions, and more pronounced tethering of tricuspid leaflets in patients with significant secondary TR compared to patients with nonsignificant TR (41,42). Presence or absence of pulmonary hypertension in secondary TR has been linked to specific patterns of RV remodeling in 2D echocardiography (28). In the presence of pulmonary hypertension, the RV remodels in the longitudinal direction (elliptical/spherical deformation) leading to increased valvular tethering with only mild tricuspid annulus enlargement.

Conversely, in isolated TR, in the absence of pulmonary hypertension, the RV has a normal length but dilates in the basal parts (conical deformation) and shows more annular enlargement (28). This predominant mechanism of annular and RA remodeling occurs mainly in patients with AF without any associated left-sided heart disease (28,29,45,46). This has been confirmed by 3D echocardiography (46), showing larger TV annulus area, larger RA dimensions, and smaller tricuspid leaflet tethering area.
in patients with chronic AF compared to patients with left-sided heart disease (46). Moreover, in patients with AF, the severity of TR may be influenced by the extent of RA remodeling, tricuspid annular dilation, and the type of AF (paroxysmal vs. persistent) (29).

**PROGNOSTIC IMPLICATIONS OF VARIOUS TYPES OF TR**

When severe TR occurs, the increase in volume overload contributes to further RV dilation and dysfunction, with further malcoaptation of the TV leaflets perpetuating a vicious circle that impacts on prognosis. One of the largest retrospective studies evaluating the association between TR grade and all-cause mortality included 5,223 patients with various grades of TR (47). During a relatively short follow-up of 1.4 ± 1.1 years, patients with severe TR had lower event-free survival rate as compared to patients with mild or moderate TR (63.9% vs. 91.7% for patients with no TR, 90.3% with mild TR, 78.9% with moderate TR) (Figure 2A) (47). Moderate and
severe TR were associated with increased all-cause mortality when the population was stratified according to clinical and echocardiographic variables (47). However, these results may not be generalizable to routine clinical practice because the study included mainly men, the assessment of TR severity and RV remodeling was based on qualitative and semi-quantitative criteria, comorbidities were not recorded or adjusted for, and the etiology of TR was not specified (47). In the last years, additional data on the prognostic implications of the various morphologic types of TR have been reported.

In primary TR, outcome studies are scarce and have been performed in retrospective observational studies. Messika-Zeitoun et al. (48) evaluated 60 patients (62% men) with significant TR caused by flail leaflets, mainly due to traumatic causes. The majority of patients were symptomatic and 33% had history of congestive HF. The presence of significant TR conferred an excess mortality of 4.5% yearly compared with the expected survival of the U.S. matched population (48).

Several studies have shown that patients who developed significant lead-induced TR after implantable cardioverter-defibrillator or permanent pacemaker implantation, presented with increased HF hospitalization and mortality rates compared to patients without significant TR (Figure 2B) (4,49,50). However, it remains unclear how often and when significant TR occurs after pacemaker implantation because the studies reporting on this complication were retrospective and the underlying mechanisms of this complication are multiple and not mutually exclusive. Therefore, the association between significant lead-induced TR and clinical outcomes may be confounded by other factors that are not taken into consideration in retrospective analyses. To further investigate the temporal relationship between significant lead-induced TR and device implantation and its clinical relevance, a multicenter prospective study is currently underway providing systematic 1-month and 1-year echocardiographic follow-up after permanent device implantation (51).

In the evaluation of the prognostic relevance of secondary TR, accurate assessment of the etiology and severity of the underlying heart disease (left-sided HF or left-sided valvular disease) is important. In a retrospective study by Hung et al. (22) including 117 patients with severely reduced LV ejection fraction, the estimated 1-year event-free survival was significantly worse in patients with mild, moderate, and severe TR versus absent or trace TR (30% vs. 68%, log-rank: p = 0.002). Similarly, among 1,421 patients with LV systolic dysfunction, the survival rate decreased with increasing grade of TR (respective 1-year and 3-year survival rates: none to mild TR, 73.4 + 1.6% and 54.6 ± 2.5%; moderate TR, 65.9 ± 3.0% and 42.1 ± 5.1%; and severe TR, 58.7 ± 4.2% and 49.0 ± 5.4%) (20). Moreover, in patients with severe aortic stenosis treated with surgical aortic valve replacement, preoperative presence of mild or moderate TR was associated with development of late significant TR, right HF and worse renal function (16).

Increased tricuspid annulus diameter was an independent predictor of late development of significant TR (16). Similarly, in a large registry including 34,576 patients with severe aortic stenosis treated with transcatheter aortic valve replacement, increasing severity of preprocedural TR was independently related to higher rates of 1-year mortality (hazard ratio [HR]: 1.29; 95% confidence interval [CI]: 1.11 to 1.50) and HF readmissions (HR: 1.27; 95% CI: 1.04 to 1.54) (Figure 2C) (52). In the presence of severe mitral regurgitation and after mitral valve surgery,
Significant TR has been related to poor outcome. Severe TR after mitral valve replacement has been associated with a 50% mortality risk at 5-year follow-up (53). In addition, in 708 patients treated with surgical mitral valve replacement, moderate-to-severe TR was independently associated with increased risk of HF events and all-cause mortality (HR: 2.17; 95% CI: 1.30 to 3.63) (54). Furthermore, in 146 patients treated with percutaneous mitral valve repair using the MitraClip device (Abbott Vascular, Abbott Park, Illinois), the presence of severe TR was independently associated with higher rates for the combined endpoint of death and rehospitalization for HF (adjusted HR: 2.67; 95% CI: 1.08 to 6.65) (55).

The underlying pathophysiology explaining the prognostic importance of secondary TR remains debated. RV dysfunction associated with significant TR is an important pathophysiologic factor determining prognosis and accurate assessment in severe TR patients remains challenging (56,57).

Finally, the clinical outcome of isolated TR has been studied by Topilsky et al. (58) in a retrospective echocardiographic study including 353 patients (33% male) in the absence of any other associated structural valve disease, pulmonary hypertension, or significant comorbidities. Overall, during a median follow-up of 5.8 ± 3.2 years, 23% of patients died and the survival rate at 10-year follow-up was 63 ± 5%.

By quantifying the grade of TR using the proximal flow convergence method (59), patients with severe

| Kaplan Meier curves for all-cause mortality are shown for patients with any type of TR (47) (A). Primary lead-induced TR (B): orange = no lead-induced TR, green = indicates significant lead-induced TR (4). Secondary TR after TAVR (C): orange = none, green = mild, blue = moderate, gray = severe (52). Isolated TR (D): orange = ERO ≥40 mm², green = ERO <40 mm² (58). ERO = effective regurgitant orifice; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation. |
TR (defined by an effective regurgitant orifice area [EROA] ≥40 mm²) showed worse survival rates compared to patients with lesser grades of isolated TR (EROA <40 mm²) (38 ± 7% vs. 70 ± 6%; p < 0.0001), independent of RV size, RV function, comorbidity, and pulmonary pressures (Figure 3D) (58). Similarly, severe TR was independently associated with lower cardiac death or congestive HF event-free survival (58). At 10-year follow-up, a trend toward worse survival and higher cardiac event rate were observed in patients with AF compared to patients in sinus rhythm (58). This latter finding may be explained by the degree of RA remodeling, which is associated with an increased risk of right HF in isolated TR in AF patients (60).

**WHAT REMAINS UNKNOWN IN TR**

Untreated severe TR is associated with poor outcomes and therefore adequate patient selection and timing for intervention are pivotal. Analysis from a large U.S. surgical database including 2,050 patients after isolated TV surgery showed high operative mortality rates (10.7%) and high major morbidity rates (61). Similarly, analysis from a large French surgical database including 241 consecutive patients undergoing isolated TV surgery (84 repairs and 157 replacements) showed high rates of in-hospital mortality (10%) and major complications (19%), which were independently associated with the preoperative degree of HF (62). These findings warrant the clinical need for earlier identification and referral of patients with severe TR at greater risk for deleterious outcomes after TV surgery. Furthermore, timing and outcome of TV surgery will also depend on the presence of significant co-existing left-sided heart disease. Recently, a clinical risk score calculator for the preoperative assessment of isolated TV surgery has been proposed that still needs external validation (61).

How can contemporary imaging techniques aid in improved risk stratification in these patients according to the morphologic type of TR? In primary TR, the level of recommendation for performing TV surgery by current guidelines depends on different criteria: TR severity (severe vs. nonsevere), symptom status, and progression of RV dysfunction during follow-up (63,64). In secondary TR, TV surgery is recommended in severe TR independent of symptom status, or may be also considered in earlier disease stages (mild or moderate TR) if tricuspid annular dilation (>40 mm) or pulmonary hypertension are present (63,64). Furthermore, reoperation for symptomatic severe secondary TR can be considered if RV function is preserved and if there is no severe pulmonary hypertension (63,64). Consequently, in a watchful-waiting strategy, contemporary imaging techniques remain the cornerstone for accurate grading of TR severity and early detection of RV dysfunction.

First, in daily clinical practice, severity of TR may still be severely underrated due to the use of qualitative parameters rather than the guideline-recommended multiparametric approach using semiquantitative and quantitative parameters (65). The first registries reporting on the safety and efficacy of transcatheter therapies for TR have highlighted the relevance of quantitative parameters to grade TR. The SCOUT (Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation) trial showed an association between reduction of a quantitative grade of TR and improvement of quality of life (66). Similarly, using the edge-to-edge repair technique through the MitraClip system, reduction in effective regurgitant orifice area was associated with an improvement of 6-min walking distance (67). To further study the relationship between the evolution of TR severity and long-term outcomes after percutaneous TV intervention, a novel quantitative TR grading system beyond classic degrees has been proposed, including a “massive” and “torrential” degree of TR (65).

Second, assessment of RV function remains challenging with current standard echocardiographic and Doppler techniques. Cardiac magnetic resonance imaging and 3D echocardiography provide a more accurate evaluation of RV dimensions and volumes and the interaction with the TV apparatus and have shown excellent intermodality correlation (68,69). Moreover, cardiac magnetic resonance imaging-derived RV ejection fraction has shown prognostic impact in the preoperative assessment for severe functional TR (70). Finally, assessment of RV longitudinal strain by speckle tracking echocardiography detects RV dysfunction earlier than conventional echocardiography and has shown incremental prognostic value in various cardiac diseases (71-75). However, outcome data of RV strain in patients with significant TR are currently lacking.

**CONCLUSIONS**

Although severe TR has been considered for years to be a surrogate of LV and RV dysfunction and pulmonary hypertension, currently the attention has shifted to the clinical and prognostic implications of severe TR. Severe TR is a rather heterogeneous valve disease that influences the clinical presentation and outcomes of many cardiac and noncardiac conditions.
Accordingly, it may be necessary to design clinical trials where the devices are tested for each specific TR and each specific clinical context. Multimodality imaging will be pivotal to select the patients with each TR morphology for each specific device.

**REFERENCES**

36. Ren JF, Callans DJ, Marchlinski FE. Tricuspid regurgitation severity associated with positioning of RV lead or other etiology assessed by

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