TRANSCATHETER TREATMENT OF TRICUSPID VALVE REGURGITATION

EDITED BY: Fabien Praz, Stefan Stortecky and Maurizio Taramasso
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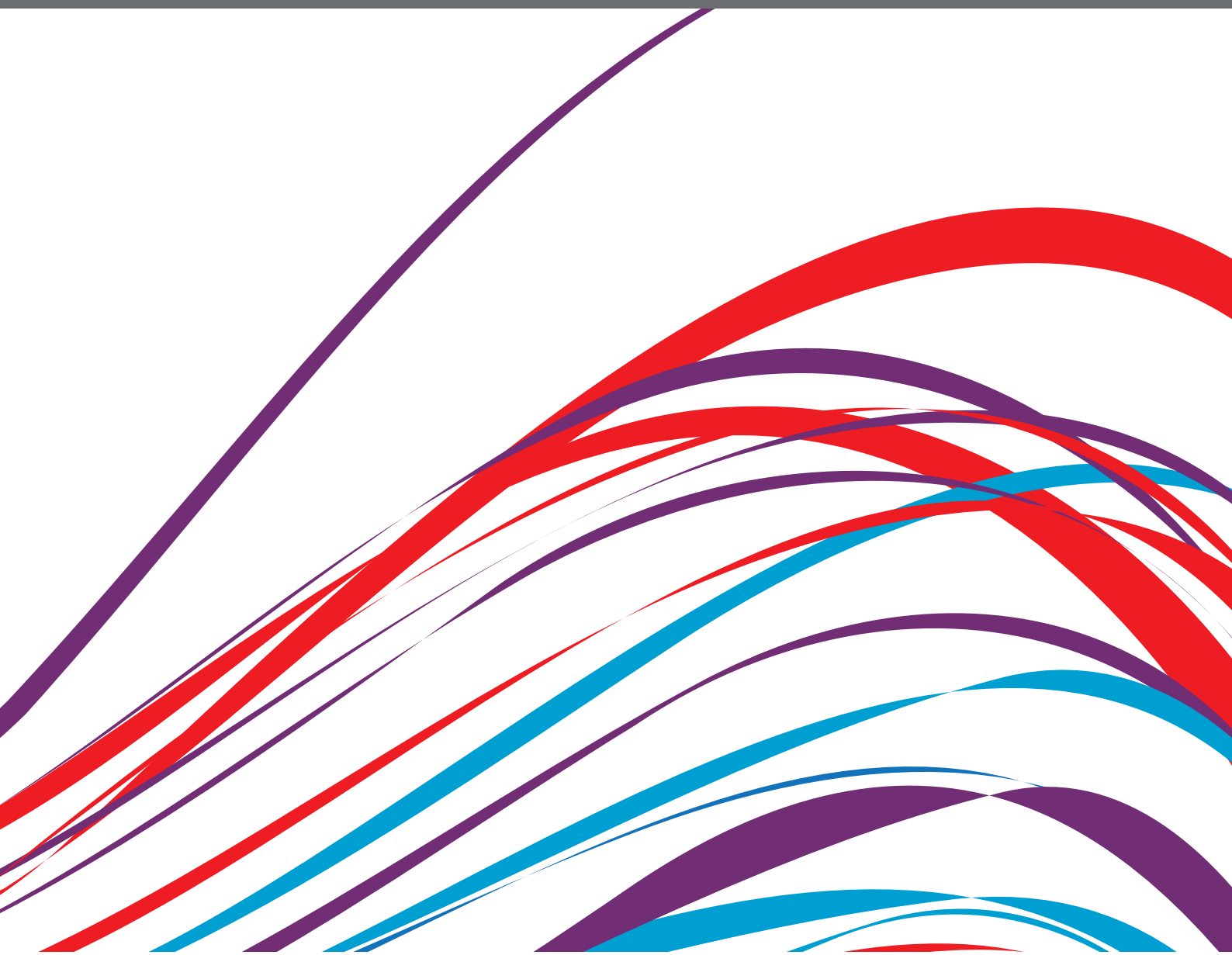

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TRANSCATHETER TREATMENT OF TRICUSPID VALVE REGURGITATION

Topic Editors:
Fabien Praz, Bern University Hospital, Switzerland
Stefan Stortecky, Bern University Hospital, Switzerland
Maurizio Taramasso, University Hospital Zürich, Switzerland

Severe tricuspid regurgitation (TR) is a common valvular heart disease with an incidence of approximately 4% in the adult general population. Most commonly, it results from secondary causes including left ventricular dysfunction, mitral regurgitation and pulmonary arterial hypertension. Isolated severe TR has been identified as an independent predictor of death and cardiac adverse events. Furthermore, TR has been observed to develop late after left-sided valve surgery in up to 10% of patients with adverse impact on clinical outcomes.

Perioperative mortality after surgical correction of TR has been reported to range between 2 and 10%. Moreover, a relevant proportion of patients with TR have already undergone open-heart surgical procedures and reoperation has been associated with an excessive risk of mortality. As a result, less invasive treatment options using transcatheter techniques may address an unmet need among high risk and inoperable patients.

Different concepts for the percutaneous treatment of symptomatic severe TR have been developed including annular reduction, restoration of coaptation, and edge-to-edge repair. Worldwide, an increasing number of patients is treated using these emerging techniques and early clinical results begin to be available.

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PERSPECTIVE
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"Guidelines Recommendations on the Treatment of Tricuspid Regurgitation. Where Are We and Where Do We Go With Transcatheter Valve Intervention"

Alec Vahanian, Eric Brochet and Jean-Michel Juliard*

Department of Cardiology, Bichat hospital, University Paris VII, Paris, France

Tricuspid regurgitation (TR) is an important clinical problem because it is frequent and carries a poor prognosis when it is left uncorrected. However, there is still a lack of awareness of tricuspid disease in the medical community. The indications for evaluation and surgical interventions in patients with TR were recently updated in the ESC/EACTS guidelines. Transcatheter tricuspid valve intervention (TTVI), almost exclusively valve repair, is at an early stage of development as only a few hundreds of patients have been treated. The first-in-man valve implantation was very recently performed. The recent ESC/EACTS Guidelines state that "The potential role of transcatheter tricuspid valve treatment in high-risk patients needs to be determined". We shall review here which lessons of interest for TTVI can be learned from the Guidelines as regards evaluation and indications for surgery and try to imagine what could be the place of TTVI in the Guidelines in the future.

Keywords: tricuspid regurgitation, transcatheter valve intervention, TTVI, guidelines, tricuspid surgery, TAVI

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Edited by:
Fabien Praz,
Inselspital - Universitätsspital Bern, Switzerland

Reviewed by:
Alexander Lauten,
Charité Universitätsmedizin Berlin, Germany
David Chistian Reineke,
Inselspital - Universitätsspital Bern, Switzerland

****Correspondence:***
Alec Vahanian
alec.vahanian@gmail.com

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INTRODUCTION

Tricuspid regurgitation (TR) is an important clinical problem because it is frequent and carries a poor prognosis when it is left uncorrected (1–7). However there is still a lack of awareness of tricuspid disease in the medical community (8).

The indications for evaluation and surgical interventions in patients with TR were recently updated in the ESC/EACTS guidelines (9). Transcatheter tricuspid valve intervention (TTVI), almost exclusively valve repair, is at an early stage of development as only a few hundreds patients have been treated (10, 11). The first-in-man valve implantation were very recently performed (12). This explains the statement in the ESC/EACTS Guidelines: "The potential role of transcatheter tricuspid valve treatment in high-risk patients needs to be determined".

We shall review here which lessons of interest for TTVI can be learnt from the Guidelines as regards evaluation and indications for surgery and try to imagine what could be the place of TTVI in the Guidelines in the future.

GENERAL COMMENTS

The recent ESC/EACTS guidelines (9) stress the importance of the awareness of tricuspid disease especially in patients with significant mitral valve disease. The patients with severe TR, especially

secondary TR, are often at an advanced stage of the disease and require a comprehensive cardiac and non - cardiac evaluation (13). The patient selection is more difficult here than for mitral regurgitation or aortic stenosis and requires expertise. As a consequence the indication for TTVI should be taken in Valve Centres, by a multidisciplinary Heart Team in order to optimize the therapeutic decision (9).

The management strategy, as advocated in the Guidelines, should follow a systematic stepwise approach trying to answer the following questions: Is the regurgitation severe? What is the mechanism of the regurgitation? Is the patient symptomatic? Are there contra-indications to any intervention on the valve? Is surgery contraindicated or high risk? Is a transcatheter intervention feasible? What is the decision of the Heart Team?

IMAGING

Imaging plays a key role. Most of the statements made in the Guidelines will apply to surgery as well as TTVI.

Echocardiography is the main examination. It assesses the "Carpentier's triade" i.e., valve anatomy, lesions and dysfunction, separating primary from the most frequent secondary TR.

It also evaluates the severity of the regurgitation using an integrative approach combining semi-quantitative and quantitative evaluation (9, 14). A new scale for severity, adding "massive and torrential" degrees, has been recently proposed but the additional prognostic value of these new grades remains to be proven (15).

More attention should be paid to the evaluation of right ventricular function (RV) using tridimensional imaging by echocardiography or cardiac magnetic resonance (CMR). CMR is considered the reference method even if precise thresholds for reversibility of RV dysfunction remain largely unknown in the field of valvular disease (9, 16, 17).

CT, which is not necessary before tricuspid valve surgery, will play a key role in the TTVI era by assessing the characteristics of the tricuspid annulus and the feasibility of each specific transcatheter techniques, in particular the relationship with adjacent structures such as the right coronary artery (18).

Right heart catheterisation should be performed when needed to evaluate the pulmonary vascular pressures/resistances because of the limitations of echocardiography in such cases.

Finally imaging during TTVI remains a challenge and the choice of one single method, or more likely multimodality imaging, should be based on new evidence (18).

Indications for Intervention

Several lessons from surgical experience should be kept in mind when considering TTVI.

As regards the choice of the technique (10), based on the surgical experience (19), the Guidelines state that "Valve repair is preferable to valve replacement. Ring annuloplasty, preferably with prosthetic rings, is key to surgery for secondary tricuspid regurgitation Valve replacement should be considered in primary TR or when the tricuspid valve leaflets are significantly tethered in secondary TR and the annulus is severely dilated".

These statements may explain why the current hemodynamic results of TTVI are suboptimal when using the first generation devices in patients with unfavourable anatomy such as very severe annular dilatation. In addition the devices currently available, such as annuloplasty or spacer, cannot treat primary TR when they are used in isolation. The feasibility of Mitraclip in degenerative TR has been documented in only a few case reports (20). In addition this technique cannot be used in patients with TR of rheumatic origin or post endocarditis. Thus awaiting more experience using combination of specific TTVI repair techniques, valve replacement may appear to be the most promising technique in primary TR. Finally the potential use of heterotopic valve implantation has to be further evaluated in the end stage disease.

The indications for TTVI in secondary TR could be expected to be as follows, with all the necessary reservations at this early stage of development.

In the near future intervention may only be considered in inoperable/high-risk patients with severe TR. Patients with severe TR after a previous mitral intervention represent the most frequent scenario. In such cases intervention should be considered early but only when it is not "futile". Severe pulmonary hypertension (21), severe LV or RV dysfunction, or significant residual left-sided valve disease should be eliminated before considering any intervention on the tricuspid valve. When RV dysfunction is "extreme", it is unlikely that any intervention on the tricuspid valve will change the prognosis (22). The guidelines did not define any precise thresholds as regards RV function for contraindicating intervention because evidence is lacking. The decision here should individualized and made by the Heart team. It is likely that the indications for TTVI might be a bit more "permissive" than those of surgery if the goal is to reduce symptoms and/or usage of drugs at an acceptable risk. In the other patients the decision will be between medical therapy or heart transplantation.

The recent ESC/EACTS guidelines insisted on the importance of an early treatment of TR, when surgery is performed only on the tricuspid valve or in combination with the surgical correction of a mitral valve disease. Mitral and tricuspid transcatheter techniques could potentially be combined in patients in the same way as in surgery. If combined transcatheter intervention is doable and affordable, TTVI should ideally be performed during the same session or early after the mitral procedure. Recent short series have suggested that it is feasible with good results (23).

In a more distant future, if both tricuspid and, even more so mitral, transcatheter intervention prove to be effective and durable in patients at lower risk, the combination of the two techniques will be even more desirable.

In patients undergoing mitral valve surgery, the Guidelines recommend tricuspid surgery in selected cases even if the degree of TR is less than severe based on the degree of annulus dilatation or progressive deterioration of RV function. These early indications cannot apply to TTVI in the near future.

Finally, the ideal approach of secondary TR caused by tricuspid annular dilatation related to chronic atrial fibrillation is largely

unexplored and the decision between the specific treatment of atrial fibrillation or tricuspid surgery or THV should be based on new evidence.

CONCLUSIONS

The role of transcatheter tricuspid intervention is likely to increase in the future based on several factors: increased awareness of tricuspid disease – improvement of technology - search for evidence. If these prerequisites are fulfilled TTVI will help transcatheter valve treatment on any valve to move towards the surgical standards.

AUTHOR CONTRIBUTIONS

AV was involved in the whole process of drafting and reviewing the Perspective, EB and J-MJ contributed with their expertise in Imaging and Surgery.

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REVIEW
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Tricuspid Regurgitation – Medical Management and Evolving Interventional Concepts

Frederik Beckhoff [1,2], Brunilda Alushi [1,2], Christian Jung [3], Eliano Navarese [4,5,6], Marcus Franz [7], Daniel Kretzschmar [7], Bernhard Wernly [8], Michael Lichtenauer [8] and Alexander Lauten [1,2]*

[1] Department of Cardiology, Charité University Hospital, Berlin, Germany, [2] German Centre for Cardiovascular Research (DZHK), Berlin, Germany, [3] Department of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, University Düsseldorf, Düsseldorf, Germany, [4] Interventional Cardiology and Cardiovascular Medicine Research, Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, Falls Church, VA, United States, [5] SIRIO MEDICINE Network, Evidence-Based Section, Falls Church, VA, United States, [6] Cardiovascular Institute, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, [7] Department of Internal Medicine, Friedrich-Schiller-University Jena, Jena, Germany, [8] Department of Cardiology, Internal Medicine II, Paracelsus Medical University Salzburg, Salzburg, Austria

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Edited by:
Fabien Praz, Universitätsspital Bern, Switzerland

Reviewed by:
Luigi Biasco, Cardiocentro Ticino, Switzerland
David Chistian Reineke, Clinic for Cardiovascular Surgery, Inselspital, Switzerland

***Correspondence:**
Frederik Beckhoff
frederik.beckhoff@charite.de

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Severe tricuspid regurgitation (TR) is a complex condition of the right ventricle (RV) and tricuspid valve apparatus and is frequently associated with symptomatic heart failure and a significant morbidity and mortality. In these patients, left heart pathologies lead to chronic pressure overload of the RV, eventually causing progressive RV dilatation and functional TR. Therefore, TR cannot be considered as isolated heart valve disease pathology but has to be understood and treated as one component of a complex structural RV pathology and is frequently also a marker of an advanced stage of cardiac disease. In these patients, medical therapy restricted to diuretics and heart failure medication is frequently ineffective. Also, severe TR in the setting of advanced heart failure constitutes a high risk for cardiac surgery. Neither one of these treatment options has demonstrated a beneficial effect on long-term prognosis. The recent innovations in transcatheter technology led to efforts to develop interventional approaches to severe TR. Multiple innovative treatment concepts are currently under preclinical and clinical investigation to replace or repair TV function. However, up to date none of these approaches is established and there is still a lack of clinical data to support the efficacy of transcatheter TR treatment.

Keywords: Tricuspid Valve Regurgitation, Interventional Therapies, The FORMA Device, Trialign, TriCinch, Traipta, Orthotopic Valve Replacement, Heterotopic Valve Replacement

1. INTRODUCTION

Severe tricuspid regurgitation (TR) is a complex condition of the right ventricle (RV) and tricuspid valve apparatus and is frequently associated with symptomatic heart failure and a significant morbidity and mortality (1, 2). In these patients, left heart pathologies lead to chronic pressure overload of the RV, eventually causing progressive RV dilatation and functional TR (3–7). Therefore, TR cannot be considered as isolated heart valve disease pathology but has to be understood and

treated as one component of a complex structural RV pathology and is frequently also a marker of an advanced stage of cardiac disease.

In these patients, medical therapy restricted to diuretics and heart failure medication is frequently ineffective. Also, severe TR in the setting of advanced heart failure constitutes a high risk for cardiac surgery (8–10). Neither one of these treatment options has demonstrated a beneficial effect on long-term prognosis. The recent innovations in transcatheter technology led to efforts to develop interventional approaches to severe TR. Multiple innovative treatment concepts are currently under preclinical and clinical investigation to replace or repair TV function (11–17). However, there is still a lack of clinical data to support the efficacy of transcatheter TR treatment. Up to date, none of these approaches gained a CE mark or FDA approval and therefore they are only meant for investigational purposes.

2. ANATOMY OF THE TRICUSPID VALVE AND THE RIGHT VENTRICLE

The tricuspid valve anatomy is very complex and has a greater variability than the mitral valve. It is composed of the fibrous annulus, three leaflets, three papillary muscles, and the chordae tendineae. It is embedded in the right ventricular inflow tract in the junction between the right atrium (RA) and the right ventricle (RV). The elliptical shaped fibrous annulus is a three-dimensional, highly dynamic structure. It is slightly larger and anatomically not as well defined as the mitral annulus. Its size and shape changes during the cardiac cycle due to contraction of the surrounding myocardium (18). The annulus provides a base for the prominent anterior, the septal and a mostly hypoplastic posterior leaflet. Valve calcification is a pathologic process but the valves are less prone to calcification compared to the mitral valve even at an advanced disease state and age. During right ventricular contraction, the annular area decreases by approximately 25–30%, which is essential for leaflet coaptation and competence of the valve (19–21). Thus, any conditions altering geometry of the tricuspid valve apparatus - such as changing loading conditions or structural enlargement of the right-sided chambers - negatively impact valve function. Adjacent to the attachment of the septal leaflet there is the AV-node and the right coronary artery encircles the valve.

3. EPIDEMIOLOGY AND PROGNOSTIC IMPACT OF TR

TR (TR) is a common insufficiency typically graded in mild, moderate and severe TR. While mild TR is frequently observed in asymptomatic persons, moderate and severe TR are seen less often (22). As even with pronounced TR many patients remain asymptomatic for several years the assessment of prevalence is difficult. In the US population, moderate-to-severe TR was estimated at approximately 1.6 million cases (23, 24).

However, as TR frequently develops with the progression of left heart or pulmonary disease, the underlying disorder rather than the tricuspid valve lesion tends to dominate the clinical picture. Increased right atrial pressure is transmitted to the central and hepatic veins leading to hepatosplenomegaly and ascites, which are present in 90% of patients with severe TR (23, 24).

Nath et. al conducted an echocardiographic series of 5,223 patients. Moderate to severe TR was found in 16% of patients (1). With increasing severity of TR mortality increased. The poor prognosis of the severe TR is independent of left ventricular ejection fraction and pulmonary hypertension (1). Several more recent studies confirmed these results and therefore underlined the correlation between severity of TR and increased mortality (25–29). In addition, patients with severe symptomatic TR showed prolonged hospitalization and a higher rate of rehospitalization (26).

4. PATHOPHYSIOLOGY

TR is most frequently "functional" in nature (8). It is commonly observed in patients with left heart valve disease, myocardial disease or pulmonary hypertension. A volume overload or/and elevated RV pressure leads to a right ventricular (RV) remodeling with RV enlargement followed by a tricuspid annulus dilatation. An increase in TV annular area develops primarily due to dilatation of the posterior and lateral segments along the right ventricular free wall (30, 31). Another mechanism of functional TR if an impaired leaflet function e.g., as in the presence of a lead crossing the TV.

In early stages RV and annulus dilatation can still be compensated and TR is not severe. A progressive dilatation leads to papillary muscle displacement and tethering of the leaflets causing severe TR. Regurgitation volume leads to increased diastolic loading which supports further RV and annulus dilatation entering a vicious circle Because right ventricular stroke volume is partially expelled backwards into the venous system, there is a resulting decrease in cardiac output and RV afterload. This decrease in right ventricular afterload in presence of TR may initially actually mask a decreased RV contractility. As right ventricular preload rises the right ventricle loses its contractility and eventually fails. As the tricuspid valve loses it function, hemodynamic parameters of the right atrium adjust to those in the right ventricle called a ventricularisation of the right atrium and finally there is a systolic backflow in the hepatic, abdominal and peripheral veins too.

Primary or non-functional TR is seen less frequent. It occurs when there is damage to the tricuspid leaflets, chordae, papillary muscles, or annulus, independent of right ventricular dysfunction or pulmonary hypertension. It can be caused by infective endocarditis, congenital disease like Ebstein anomaly or atrioventricular canal, rheumatic fever, carcinoid syndrome, endomyocardial fibrosis, myxomatous degeneration of the tricuspid valve leading to prolapse, penetrating and non-penetrating trauma, and iatrogenic damages during cardiac surgery, biopsies, and catheter placement in right heart chambers

TABLE 1 | Grading the severity of TR.

	Mild	Moderate	Severe
Structural			
TV morphology	Normal or mildly abnormal leaflets	Moderately abnormal leaflets	Flail leaflet, large coaptation defect, severe retraction, large perforation
RV size	Normal	Normal or mild dilatated	Dilatated
RA size	Normal	Normal or mild dilatated	Dilatated
VCI diameter (cm)	<2	2–2,5	>2
Qualitative Doppler			
Color flow jet area	Small, narrow, central	Moderate central jet	Very large central jet or eccentric wall impinging jet
Flow convergence zone	Not existent	Intermediate in size and duration	Large throughout systole
CW signal of jet	Faint/partial/parabolic	Dense, parabolic or triangular	Dense, triangular with early peaking (peak ,2 m/s in massive TR)
Semiquantitative			
Color flow jet area (cm^2)	Not defined	Not defined	>10
VCW (cm)	<0.3	0.3–0.69	≥0.7
PISA radius (cm)	≤0.5	0.6–0.9	>0.9
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal
Tricuspid inflow	A-wave dominant	A-wave dominant	E-wave >1.0 m/sec
Quantitative			
EROA (cm^2)	<0.20	0.20–0.39	≥0.40
R Vol (ml)	<30	30–44	≥45

Based on the 2010 guidelines by the European Society of Echocardiography and the 2017 guidelines by the American Society of Echocardiography (32, 33).
CVI, vena cava inferior; CW, continuous-wave; EROA, effective regurgitant orifice area; R Vol, regurgitant volume; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve; VCW, vena contracta with.

(3, 32). These entities lead to billowing valve, a prolapse or a flail tricuspid valve.

5. DIAGNOSIS OF TR

5.1. Echocardiography

Echocardiography is the main tool to confirm the diagnosis, determine aetiology and assess the severity of TR. Color flow imaging can be used as a screening method. Grading of the severity should be performed in accordance to the guidelines published in 2010 by the European Society of Echocardiography and in 2017 by the American Society of Echocardiography (32, 33).

These guidelines recommend several structural, qualitative, semiquantitative and quantitative parameters (**Table 1**). A simple parameter that is easy to obtain and well validated is the vena contracta width (VCW). It is usually obtained in the four-chamber view using color flow imaging. The VCW is measured perpendicular to the commissural line at the narrowest portion of the jet reflecting the regurgitant orifice area. A VCW > 7 mm indicates a severe TR. Lower values are difficult to interpret and therefore should not be used to distinguishing moderate from mild or severe TR. Using a continuous wave (CW) Doppler in the four-chamber view at the tricuspid leaflet tips the TR can be further evaluated. In case of a severe TR the WC signal is intense, truncated and triangular indicating an elevated right atrial pressure. The peak E velocity representing the early diastolic filling increases in the proportion to the degree of TR. A peak E Velocity >1 m/s suggests a severe TR. The proximal isovelocity surface area (PISA) is measured in the apical four chamber view and in the parasternal long axis. Nyquist limit must be lowered to 28 cm/s. PISA radius is than measured using the first aliasing. A PISA radius >9 mm indicates a severe TR whereas a radius <5 mm indicates a mild TR. After calculating the PISA the effective regurgitant orifice area (EROA) and regurgitations volume (Rvol) can be calculated using the time velocity integral in the continuous wave Doppler (CW) signal. An EROA ≥40 mm2 or a Rvol ≥45 mL indicates severe TR.

In moderate to severe TR evaluation of the RV and RA dimensions, RV function and the venous congestion is mandatory. The tricuspid annular plane systolic excursion (TAPSE) is easy to obtain and well validated to assess the right heart function. A TAPSE <17 mm is highly suggestive of RV systolic dysfunction.

The right heart dimensions have previously been published in an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging (34). Measurements should be performed in multiple acoustic windows but the most important view is the four-chamber view focused on the RV. In this view, the left apex is in the center of the scanning sector and the largest basal RV diameter is displayed. In this view, a diameter >41 mm at the base and >35 mm at the midlevel in the RV-focused view indicates RV dilatation. The RV longitudinal diameter ranges between 59–83 mm, and therefore a dilatation is present if the longitudinal diameter exceeds 83 mm. Normal diastolic tricuspid valve annulus diameter is 22–33 mm and a significant annulus dilatation is present when the diameter exceeds 21 mm/m^2 (>40 mm).

The right atrium is assessed in the same echocardiographic window. Mostly performed are linear and volume measurements. Linear measurements include the minor and the major axis of the LA. The minor axis is should be measured as the distance between the lateral RA wall and interatrial septum in the midatrial level. A normal value is 1.9 cm/m^2. The major axis is orthogonal to the minor axis and is normally between 2.4–2.5 cm/m^2. The more accurate RA volume is 21–25 mL/m^2.

The atrial pressure can be estimated by the use of vena cava diameter and the percentage of decrease of diameter during inspiration. An IVC diameter <2.1 cm with a collapse >50% during inspiration suggests normal RA pressure of 3 mm Hg, whereas IVC diameter >2.1 cm that collapses <50% during inspiration suggests high RA pressure of 15 mm Hg (35). In cases where IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg should be assumed (34). Hepatic veins are an additional tool grading the TR. Using color flow or pulsed wave Doppler (PW) a systolic flow reversal can be observed in patients with severe TR.

6. CURRENT THERAPY AND ITS LIMITATIONS

6.1. Currently Recommended Treatment and Their Indications

Currently medical and surgical therapy are the only established treatments options for patients with severe TR. Medical treatment is considered a symptomatic therapy limited to diuretics. Surgical repair or replacement is associated with a significant mortality and is therefore restricted to a selected group of patients with a suitable risk profile. Also, the timing for surgery remains controversial (36). According to the ESC/EACTS guidelines, patients with primary TR should undergo surgery even when still asymptomatic or when undergoing surgery for left-sided valvular heart disease. In contrast, secondary severe TR is only surgically corrected when patients undergo left-heart surgery. However, these guideline recommendations are Level C recommendations due to the lack of data. Although these patients respond well to diuretic therapy medical treatment should not delay surgery to avoid secondary damage in terms of irreversible RV dysfunction which is associated with worse outcome.

6.2. Surgical Therapy

Today surgical correction of TR focuses on restoring valve function by reducing annular size. However, the efforts to achieve the most durable results have resulted in an ongoing debate as to whether annular plication should be achieved by implanting either flexible or rigid rings rather than by means of a partial purse string suture technique ("DeVega-technique"). Rigid annuloplasty rings appear to have a lower incidence of recurrent TR than flexible devices or the DeVega technique. In addition, the edge-to-edge tricuspid valve repair has been suggested as providing an effective adjuvant procedure for severe residual TR following annuloplasty (37, 38). The procedure is analogous to mitral valve repair by leaflet approximation and involves anchoring the anterior leaflet to the facing edges of the septal and posterior leaflets of the tricuspid valve, thus creating a triple orifice. Prosthetic TV replacement is reserved for advanced structural valve disease and carries a higher perioperative risk compared to valve repair. Following tricuspid valve replacement, a lower 10 year survival rate has been reported compared to TV replacement (37–4.8% versus 47.5–3.5%) (39).

6.3. Current Interventional Approaches

Patients with severe TR are frequently considered inoperable due to comorbidities and surgery is therefore often refused (40, 41). Thus, there is a large unmet need for less invasive treatment options. Recently, the tricuspid valve is receiving much attention from interventional cardiologists and industry, seeking to develop novel catheter-based approaches to TR. So far most of these treatments have been applied in compassionate human cases or small feasibility trials and limited experimental data have been published. Transcatheter TR repair concepts are focusing to reproduce surgical concepts such as annuloplasty or leaflet adoption, but also alternative approaches are under investigation such as coaptation enhancement or heterotopic caval valve implantation (**Figure 1**).

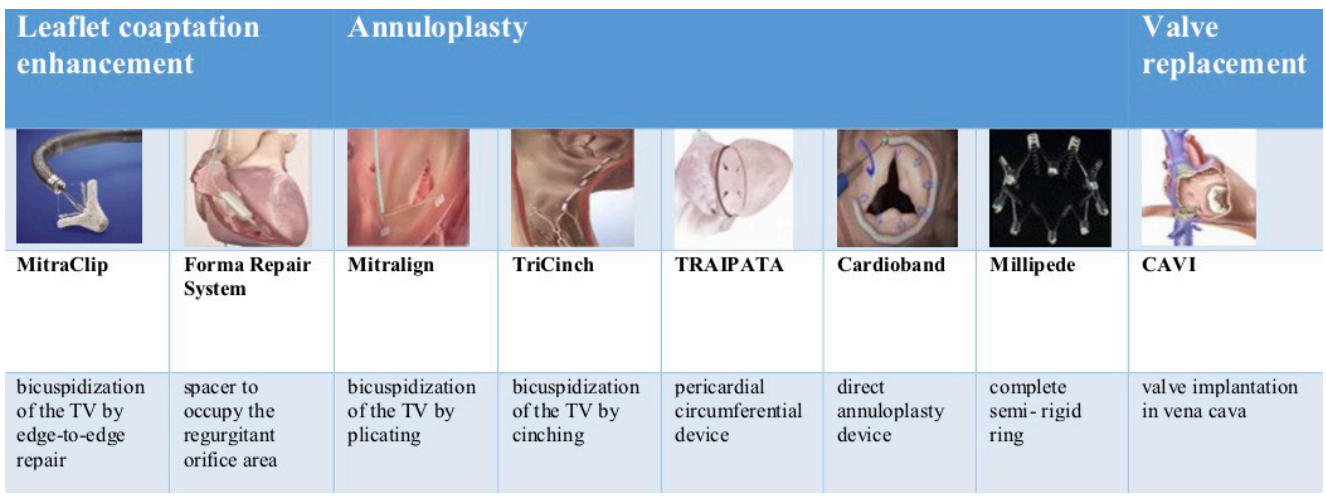

FIGURE 1 | Overview over new tricuspid valve repair devices. CAVI, caval valve implantation; TV, tricuspid valve; TRAIPTA, transatrial intrapericardial tricuspid annuloplasty.

6.3.1. Leaflet Enhancement

6.3.1.1. The FORMA Device (Edwards Lifesciences)

The FORMA Repair System (Edwards Lifesciences) has been designed for patients with a severe functional TR. Annulus dilatation leads to malcoaptation of leaflets and therefore to a central regurgitant jet. By advancing a spacer in the center of the regurgitant yet the regurgitant orifice area is occupied and leaflets have a new coaptation surface. Therefore, the TR Grade can be reduced. The spacer is a foam-filled polymer balloon that passively expands via holes in the spacer shaft. It is available in 12 and 15 mm both with a length of 42 mm. Two radiopaque markers help to initially position the spacer using fluoroscopy. The distal end is connected to a rail anchored at the apex of the RV whereas the proximal end is locked in the subclavian region with the extra rail length coiled into a pre-pectoral pocket.

The first in men experience with the FORMA device was published in 2015. Seven high-risk patients with severe TR presenting with clinical signs of heart-failure deemed unsuitable for surgery received the FORMA device as a compassionate use. All patients had a New York Heart Association (NYHA) functional class II to IV. Device implantation was successful without procedural complications in all patients. Severity of TR could be reduced significantly to moderate TR in 3 patients and to mild TR in 4 patients. At 30 day follow-up, all patients but 1 demonstrated an improvement in NYHA functional status to class II. No complications related to the device or vascular access were observed during follow-up (42). Recently the one-year experience from eighteen patients at 3 centers in Canada and Switzerland with the transcatheter FORMA system was published. They presented a good mid-term safety profile. Despite variable success in reducing echocardiographic TR grade, there were significant clinical improvements and reductions in right ventricular dimensions (43).

The FORMA system is an investigational device and not for sale in any country. An Early Feasibility Study is currently recruiting patients in the USA (NCT02471807). The 30 day data of the US feasibility trial were presented at the TCT 2017 by Susheel Kodali, MD (NewYork-Presbyterian/Columbia University Medical Center, New York, NY). 30 patients with severe symptomatic TR from five US centers underwent implantation of the Forma device. All in all, the results proved that the device is a feasible therapy for patients with severe TR. Nevertheless, it was associated with infrequent distal anchor dislodgements and the complications thereof. The next generation of this device probably with a more predictable anchor capture without dislodgement or RV perforations is already under development.

Beside the Early Feasibility Study in the USA other multicenter trials are planned in Europe and Canada.

6.3.1.2. MitraClip in Tricuspid Position

The MitraClip® system has been invented for high risk patients with mitral regurgitation which are unsuitable for surgery. It is a procedure that involves the percutaneous implantation of one or more clips grasping and approximating the edges of the leaflets at the origin of the regurgitant jet and therefore reducing it. In 2011, this procedure was presented first time by Feldman et al (44). Until today this has now been integrated in the clinical routine for patients with severe mitral regurgitation at high risk constellation. In 2016, the first clips could successfully be implanted at the tricuspid valve (45). In 2017, Nickenig et al demonstrated the feasibility and safety of leaflet coaptation using the MitraClip in tricuspid position in 64 consecutive patients (46). In this report clips where implanted in multiple commissural sites, while now the strategy is to perform a bicuspidization of the tricuspid valve by a progressive clipping of the septal and anterior leaflet until satisfactory reduction of TR is achieved as well as the gradient across the valve is not increased significantly.

Nevertheless, clipping the tricuspid valve is more difficult than performing a clip in mitral position. The angle between the IVC and the TV annular plane makes coaxial positioning difficult. A transjugular approach has been described but the femoral approach was favored in the above-mentioned study.

6.3.2. Annuloplasty

6.3.2.1. Trialign

The Trilign device (Trialign, Tewksbury, Massachusetts) is a percutaneous minimal invasive annuloplasty system initially designed for the treatment of symptomatic functional mitral regurgitation. First experiences have been made with the treatment of patients with severe tricuspid regurgitation. It was inspired by the Kay bicuspidization procedure, in which the annulus is plicated along its muscular part adjacent to the posterior leaflet (47). With the help of an 8 F articulating wire delivery catheter and a pledget delivery catheter using a transjugular venous approach, pledgets with sutures are fixed at the anteroposterior and septoposterior commissures. These steps are guided by TEE and fluoroscopy. Afterwards a plication lock device is used to bring the 2 pledgeted sutures together, plicating the annulus and effectively bicuspidizing the tricuspid valve.

The first-in-man procedure was published in 2015. The Trialign device was implanted in an 89-year-old woman with right heart failure due to TA dilation and severe TR as a compassionate use. After procedure, there was a significant reduction of tricuspid annulus area (57%) and effective regurgitant orifice area (53%). Hemodynamic parameters in terms of right atrial pressure and left ventricular stroke volume also improved (48). There are two ongoing early feasibility studies, one in the USA (NCT02574650) and one in Europe (NCT03225612). The 30 day results of early feasibility trial in the USA were recently published. The results confirmed the safety of the novel transcatheter device, which reduced tricuspid annulus diameter, effective regurgitant orifice area, increased the left ventricular stroke volume, and improved quality-of-life measurements (49).

6.3.2.2. TriCinch

The TriCinch System (4Tech Cardio Ltd., Galway, Ireland) is a percutaneous device designed to reduce functional TR by reducing the septo-lateral distance. It is composed of two parts: a stainless-steel corkscrew and a self-expanding nitinol stent. Both are connected by a Dacron band. First, the corkscrew is delivered by a delivery system from the Inferior Vena Cava and fixated at the anteroposterior TV annulus. After the delivery system is removed a second delivery system is advanced containing the other half of the TriChinch System. Both Dacron bands are now connected with a locking mechanism. By pulling the TriChinch System tension is applied to the TVA and therefore the septo-lateral distance is

reduced. If echocardiography shows the desired reduction of TR, the stent is deployed in the inferior vena cava to maintain the tension.

Four stent sizes are currently available (27, 32, 37, and 43 mm).

The "first-in-man" procedure was reported in 2015. The patients was a 72-year-old woman enrolled in the PREVENT (Percutaneous Treatment of Tricuspid Valve Regurgitation With the TriCinch System; NCT02098200) study. She had a severe functional TR associated with tricuspid annular dilation causing multiple hospitalization. New York Heart Association functional class was III. The procedure was completed in 56 min and the patient was discharged 5 days later. No intra- or postprocedural complications were observed. TR grade could be reduced from grade 4 to grade 3. The 6 month follow-up showed an improved quality of life.

At this time, enrollment of 24 patients in the PREVENT Trial is completed. Results are not published yet.

6.3.2.3. TRAIPATA

The transatrial intrapericardial tricuspid annuloplasty (TRAIPTA) is a minimal invasive device for patients with functional TR. Once implanted it acts as a epicardial annuloplasty band. After a transfemoral venous approach pericardial access is obtained by puncturing the right atrial appendage.

Once the delivery device is advanced in the epicardial space it opens a preformed loop that is passed around the apex of the heart and then retracted toward the base. Finally it can be tightened at the atrioventricular groove. After the procedure, the right atrial appendage must be closed with a percutaneous occluder device.

The device has not yet been implanted in humans but it was applied in 16 Yorkshire swines, including 4 with functional TR. Tricuspid septal-lateral and anteroposterior dimensions, the annular area and perimeter was significantly reduced. Small postprocedural effusions (mean, 46 ml) resolved completely at follow-up. There is no other trial registered at Clinical Trials.

6.3.2.4. Cardioband

The Cardioband repair system (Edwards Lifesciences) is an approved treatment of secondary (functional) mitral regurgitation (FMR). It has been recently used in a clinical trial in patients with severe tricuspid regurgitation caused by a dilatation of the right annulus. The cardioband system is a catheter-based device that functions as a percutaneous annuloplasty band using a transfemoral approach. Implantation of the Cardioband is performed by stainless steel anchors (6 mm long). After cinching of the Cardioband the device reduces the tricuspid annular dimensions. Studies are currently investigating the use of the Cardioband in tricuspid regurgitation (NCT02981953, NCT03382457).

6.3.2.5. Millipede IRIS Transcatheter Annuloplasty Ring

The IRIS is a complete semi-rigid annuloplasty ring that is placed via a transfemoral venous approach. After puncture of the femoral vein a delivery catheter is advanced into the right atrium. The delivery catheter places the device supra-annularly and the ring is then anchored and cinched reducing annular size and therefore valvular regurgitation. Up to date annuloplasty device is only studied in patients with mitral regurgitation (NCT02607527).

6.3.3. Valve Replacement

6.3.3.1. Orthotopic Valve Replacement

The tricuspid annulus is a complex and highly dynamic structure offering little resistance for long-term fixation of orthotopic valves. Particularly under conditions of severe TR the annulus is massively dilated with a loss of anatomic landmarks. Therefore, the development of transcatheter orthotopic valve implantation is associated with specific challenges, including device fixation, paravalvular sealing, sizing and thrombogenicity in a low-flow, low-pressure circulation. The NaviGate transcatheter tricuspid valve has been developed for orthotopic correction of severe functional TR by "NaviGate Cardiac Structures Inc.. The bioprosthetic self-expanding valve with a size of up to 52 mm has been implanted successfully in compassionate cases (50).

6.3.3.2. Heterotopic Valve Replacement

Severe TR leads to a systolic backflow in the hepatic, abdominal and peripheral veins causing peripheral oedema, liver cirrhosis, ascites and gastrointestinal dysfunction. Implanting a prosthetic valve in the central venous system (caval valve implantation = CAVI) reduces the venous congestion leading to amelioration of peripheral signs of right heart failure (51). Heterotopic valve implantation can be performed as single valve in the IVC or as dual valve in the IVC and SVC. The major challenges to valve implantation are the variable and large diameter of the vena cava inferior and superior and the short distance between the right atrium to the hepatic veins. "First-in-man" implantation of a self-expanding customized prosthetic valve in the IVC was reported in 2011 (51). The patient was a 79-year-old female with severe functional TR considered inoperable due to multiple previous open-heart surgeries. The patient had suffered from progressive symptoms of RV congestion with peripheral oedema, liver cirrhosis, and persistent ascites with gastrointestinal dysfunction. Procedure was performed under general anesthesia in a hybrid operating room. The prosthetic valve was delivered from the right femoral vein with a custom-made 27 F implantation catheter. After satisfactory position was confirmed by fluoroscopic and echocardiographic visualization valve was released from catheter. There were no intra- and postprocedural complications. After deployment, excellent function of the device was observed and echocardiography showed a nearly abolished ventricular wave after valve deployment. During follow-up the patient experienced a gradual improvement of symptoms related to venous congestion and right heart failure. Despite the promising data from compassionate use of the CAVI procedure data demonstrating clinical efficacy is still lacking. A recent observational trial in 25 patients demonstrated the safety and hemodynamic efficacy of CAVI using either the IVC-only or the BiCAVI approach (52). For CAVI only a few valves are suitable. The percutaneous valve system (Tric Valve, P&F GmbH, Vienna, Austria) has been developed for the bicaval venous implantation (**Figure 2**). It is composed of two separate three leaflet pericardial tissue valves reaching from 28 to 43 mm. Beside the Tric Valve balloon-expandable valves (BEV) like the commercial available Edwards Sapien XT and Sapien 3 can be used. These valves are designed for treatment of aortic stenosis (29 mm Edwards Sapien XT or Sapien 3; Edwards Lifesciences, Irvine, CA), but there is a growing experience in the off-label use of these devices for treating severe TR. Because of the large diameter of the cavoatrial junction,

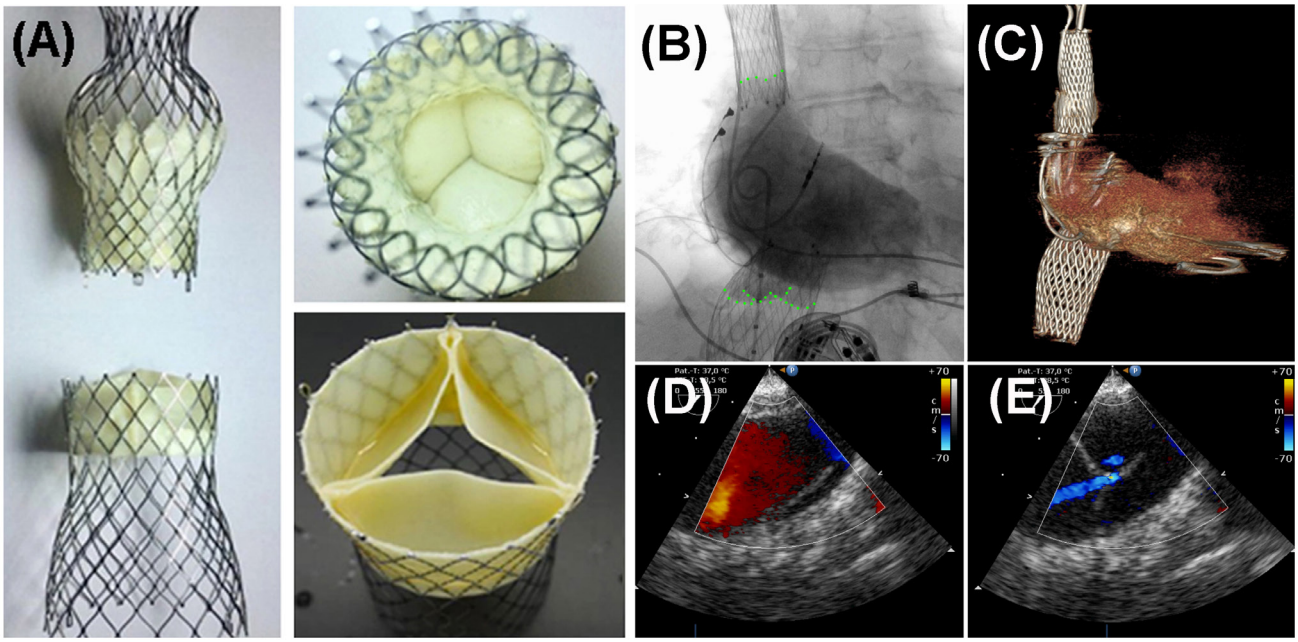

FIGURE 2 | Caval Valve Implantation (CAVI) using balloon-expandable valves (SEV). **(A)** The TricValve-SEV, an investigational device with two designated valves for SVC and IVC position has been used for CAVI. **(B, D, E)** An angiogram of the right atrium and transesophageal echo demonstrates function of both valves. **(C)** Position of both valves is visualized by CT.

the inflow of hepatic veins and the compliance of the venous wall direct implantation of a BEV and requires the preparation of a landing zone by implanting a self-expandable stent to facilitate valve fixation. A CAVI using BEV is mostly performed only in the IVC but it can also be implanted in the IVC and SVC as a BiCAVI approach. After implantation of a heterotopic valve in the low-pressure system a lifelong anticoagulation will be required irrespective of the valve type.

7. CONCLUSION

The management of patients with severe symptomatic TR remains challenging. As patients are frequently referred for surgery late in the disease process this treatment is associated with an excessive morbidity and mortality. On the other hand, medical therapy, consisting primarily of escalating doses of diuretics is frequently ineffective as patients develop increasing diuretic resistance secondary to worsening renal function. Therefore, interventional treatment approaches are needed and multiple devices are in preclinical and clinical stages of investigation.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Comparative Anatomy of Mitral and Tricuspid Valve: What Can the Interventionlist Learn From the Surgeon

Alberto Pozzoli[1]*, *Michel Zuber*[1], *Mark Reisman*[2], *Francesco Maisano*[1] and *Maurizio Taramasso*[1]

[1] Heart Valve Clinic, University Hospital of Zurich, University of Zurich, Zurich, Switzerland, [2] Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA, United States

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***Correspondence:**
Alberto Pozzoli
alberto.pozzoli@usz.ch

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Transcatheter valve interventions on the mitral and tricuspid valves entail increasing complexity. Part of the knowledge that has been generated during the development of mitral devices can be transferred to the tricuspid valve (TV). However, a deeper understanding of the peculiar anatomy of the TV and of the right heart chambers, together with differences and similarities between the two valves, is fundamental. This report compares the anatomy of the mitral and tricuspid valves, and its inferences with regard to transcatheter treatments.

CONDENSED ABSTRACT

This report explores anatomical similarities and differences between the mitral and the tricuspid valves, and their implications with regard to transcatheter treatments.

Keywords: tricuspid valve, mitral valve, transcatheter therapies, comparative anatomy, multimodality imaging

INTRODUCTION

Transcatheter valve therapies deeply changed the treatment of heart valve disease over the last decade. Shifting from aortic valve interventions (TAVI), more reproducible and with less anatomical variables, toward the AV valves entails increasing complexity and deeper knowledge of these two valves. The development of transcatheter mitral valve (MV) therapies was much more slower, mainly due to the structure and complexity of the MV apparatus and its pathology. With the development of transcatheter tricuspid valve (TV) therapies, interventionists are dealing with an even more stimulating anatomical scenario. Part of the knowledge that has been generated during the development of mitral devices can be transferred to the TV. Therefore, a deep knowledge of the tricuspid anatomy and of the right heart chambers, comparing the differences between the two AV valves, becomes fundamental (1). In this report, the anatomical similarities and differences between mitral and tricuspid apparatus, and their impact (effect) with regard to transcatheter treatments (**Table 1**) will be addressed.

LEFT ATRIUM, RIGHT ATRIUM, AND INTERVENTIONAL ACCESS

Anatomical Description

Left Atrium

The left atrium (LA) is the cardiac chamber that normally receives pulmonary venous drainage from the four pulmonary veins. Its septal surface is characterized by the flap valve of the fossa ovalis (septum primum), in contrast to the limbus (septus secundum) of the fossa ovalis present on the right atrioseptal surface (**Figure 1**).

Right Atrium

The right atrium (RA) consists of a curved posterior groove continuous with the superior and inferior venae cavae, a flat interatrial septum, a trabeculated dome, and the TV. In comparison to the LA, the RA has thinner walls and dilates more easily given the same degree of pressure overload.

Interventional Considerations

Different interventional accesses to the LA have been adopted, including direct transatrial, transapical, transarterial retrograde, and transseptal.

Transatrial and transarterial retrograde routes are currently used only in really specific situations and have almost been abandoned.

The transseptal access, through the inferior vena cava favored by the crista dividends, is currently the preferred route for most transcatheter MV repair techniques and its usage is quickly increasing for mitral valve-in-valve and valve-in-ring procedures, since it showed superior safety compared to the apical one (2, 3). Transapical access is the most used approach for native MV replacement and for transcatheter neo-chordal implantation, and it will be discussed below in the section describing the ventricles.

Transseptal catheterization is a safe and well-known approach to the LA and, therefore, to the MV. As an example, transseptal route is used for MitraClip (Abbott Vascular, USA) and for direct annuloplasty with the Cardioband device (Edwards Lifescience, USA). Both of the devices are delivered through a big (24F) steerable guiding catheter, which allows the operator to reach the anatomical therapeutic target with a high level of precision, required to ensure safety and efficacy.

Therefore, to guarantee the needed precision, the location of the transseptal puncture is essential, since a specific therapeutic target could be extremely challenging or even impossible to reach with a proper trajectory, if the puncture is performed in a wrong location. To this aim, operators should be familiar with the anatomical structures in proximity to the interatrial septum: in case of a too anterior or too posterior puncture, the ascending aorta or the posterior LA wall, respectively, can be punctured and injured. Procedural imaging with TEE is the key to perform precise and safe transseptal puncture in complex structural interventions. Once the guiding catheter has been introduced in the LA through the interatrial septum, the septum gives the catheter itself adequate support and optimal stabilization, which allow the operators a really controlled and predictable steering of the guiding catheter.

Navigation in the LA can be extremely challenging and potentially dangerous in presence of a small LA, due to reduced degrees of movements, with increased risk of perforation, impingement, and bleeding. The structures at higher risk are the LAA and the pulmonary veins. In particular, the LAA is located anteriorly to the fossa ovalis, and it is easy to reach when crossing the septum if the atrium is not enlarged.

Similarly to the mitral valve, the tricuspid is commonly approached anterogradely. Currently, the most used approach is the transfemoral one through the inferior vena cava (IVC) (MitraClip, Cardioband, TriCinch), whereas some devices are delivered through a transjugular approach (Trialign, Forma).

Since the TV is approached directly without transseptal puncture, the support provided by the interatrial septum to the catheter in transseptal MV procedures is missing, resulting in a complete lack of stabilization. The absence of the septal support results in diving into the right ventricle (RV) and lack of coaxiality. This represents a major issue, making navigation in the RA more challenging and less controlled.

MITRAL AND TRICUSPID ANNULI

Anatomical Description

The Mitral Annulus

The mitral annulus is reinforced at each extremity of the base of the anterior leaflet, by two dense triangular fibrous structures: the antero-lateral (or left) and the postero-medial (or right) fibrous trigones (**Figure 2**) (2). Very important, the MV annulus has a 3D saddle-shape configuration and its shape varies through the cardiac cycle (3). Four anatomical structures close to the mitral annulus are at risk of injury during interventional procedures:

(I) The circumflex artery, which runs posteriorly and could be injured, especially during annuloplasty;
(II) The coronary sinus, which skirts the attachment of the posterior leaflet;
(III) The bundle of His which is located near the right trigone (medial commissure);
(IV) The non-coronary and left coronary aortic cusps which are in close relationship with the base of the anterior leaflet, the so-called mitro-aortic fibrous continuity (there is a 6–10 mm safety zone in this area).

The Tricuspid Annulus

The right AV Junction delineates the change between the RA and the TV leaflets (**Figure 3**). Contrarily to the mitral one, the tricuspid annulus is tiny and difficult to identify and delimitate; annular calcifications are almost absent. In pathologic conditions, such as long lasting tricuspid regurgitation (TR), the TV annulus tends to become planar (4, 5).

Abbreviations: AV, atrio-ventricular; TAVI, transcatheter aortic valve implantation; MV, mitral valve; TV, tricuspid valve; LA, left atrium; RA, right atrium; LAA, left atrial appendage; RAA, right atrial appendage; TEE, transesophageal echocardiography; TTE, trans-thoracic echocardiography; ICE, intra-cardiac echocardiography; LV, left ventricle; RV, right ventricle; PM, papillary muscle; LVOT, left ventricle outflow tract; RVOT, right ventricle outflow tract.

TABLE 1 | Similarities and anatomical differences between mitral and tricuspid valve apparatus, and their implications with regard to transcatheter treatments.

Left ATRIUM and LAA	**Right ATRIUM and RAA**	**Interventional considerations**
• Thicker walls than the RA • Smooth atrial cavity • Long and narrow trabeculated LAA • Presence of PVs orifices	• Thinner and more distensible walls • Presence of Crista Terminalis • Wide and blunted RAA • Presence of SVC, IVC, and CS orifices	• RA is reached either from SVC or IVC • LA is reached mostly through the septum and provides support to device delivery system • Higher chance of LAA perforation
Mitral ANNULUS	**Tricuspid ANNULUS**	**Interventional considerations**
• Attached to 2 fibrous trigones (AL-PM) • Saddle-shaped in systole • Fibrous structure is thick • Contiguity with the His bundle (PM commissure), the coronary sinus and the Cx artery (posterolateral region)	• Attached to only 1trigone (PM) • Easily distensible with thinner and almost virtual fibrous structures • Largest orifice of all valves (7–9 cm) • Contiguity with the Koch triangle, RCA (anteroposterior) and aortic cusps	• TV annular procedures are most prone to injury the RCA (longer course), the AV node and His bundle (AV block) and the aortic cusps (AR) • TV imaging guidance is more challenging ("TEE-unfriendly," ICE frequently needed) • Complete obliteration of EROA and valve sealing is cumbersome in tricuspid position
Mitral LEAFLETS and COMMISSURES	**Tricuspid LEAFLETS and COMMISSURES**	**Interventional considerations**
• 2 leaflets (A-P) and 2 commissures • Thicker and more resistant than TL	• 3 leaflets (A-P-S) and 3 commissures • Thinner, translucent and more fragile	• Higher chance to damage or tear the TV leaflets
Mitral CHORDAE TENDINAE	**Tricuspid CHORDAE TENDINAE**	**Interventional considerations**
• Thicker and more resistant. • Bifurcated/trifurcated at the free edge • Extend directly from the heads of PMs	• Thinner and more fragile • Single attachment at the free edge • Originating from various level of PMs and can attach directly to the RV wall	• High chance of entrapment and impinging the commissural chordae, once the valve is crossed • Higher risk in the AS commissural region of the TV
Mitral PAPILLARY MUSCLES	**Tricuspid PAPILLARY MUSCLES**	**Interventional considerations**
• 2 papillary muscles (AL-PM) • Single bulky or multiple heads • No PMs is attached to the septum	• 3 papillary muscles (ANT dominant- POST-SEPT, multiple and thinner heads) • Can originate from the septum	• Higher chance of catheter entrapment, especially in the antero-septal commissural region
Left VENTRICLE and LVOT	**Right VENTRICLE and RVOT**	**Interventional considerations**
• Thicker walls than the RV (3:1) • Absence of Moderator Band • MV is in continuity with the AV through the mitro-aortic curtain cohoctic cavity	• Thinner and more distensible walls (1:3) • Presence of Moderator Band • TV and PV are widely separated • Crescentic cavity	• Increased risk of LVOTO during TMVR • Risk of RVOTO is negligible/absent • RV transapical access suboptimal for coaxiality and potentially risky in thin,dilated RV

RA, right atrium; LA, left atrium; RAA, right atrial appendage; LAA, left atrial appendage; PVs, pulmonary veins; MV, mitral valve; TV, tricuspid valve; PV pulmonary valve; SVC, superior vena cava; IVC, inferior vena cava; CS, coronary sinus; AL, anterolateral; PM, posteromedial; A, anterior; P, posterior; S, septal; AS, anteroseptal; Cx, circumflex artery; RCA, right coronary artery; AR, aortic regurgitation; TEE, transesophageal echo; ICE, intracardiac echocardiography; EROA, effective regurgitant orifice area; PMs, papillary muscles; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; TMVR, transcatheter mitral valve replacement; RV, right ventricle; AV, aortic valve. This table has been adapted from Taramasso et al. (1).

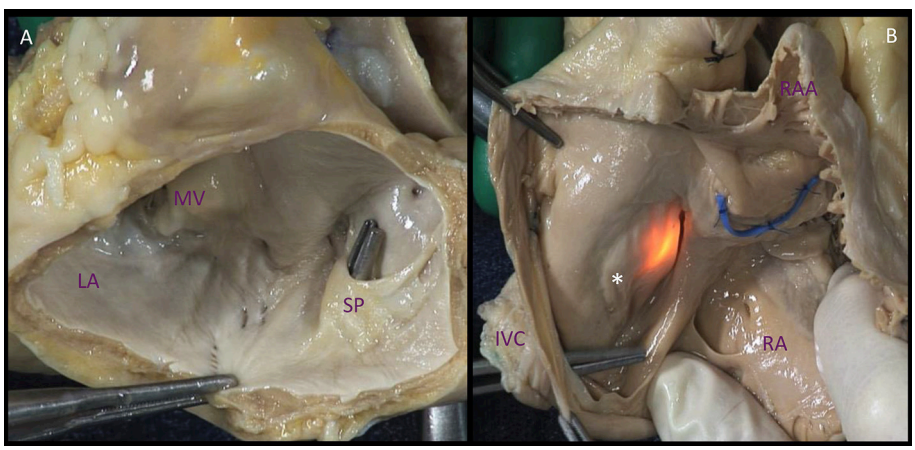

FIGURE 1 | Comparison of the atrial septal surfaces. **(A)**. The septal surface of the left atrium is characterized by the flap valve of the fossa ovalis (septum primum), in contrast to the limbus of the fossa ovalis (*) present on the right atrioseptal surface **(B)**. The source of light indicates the fossa ovalis, the blue band depicts the position of the aortic non-coronary sinus. LA, left atrium; MV, mitral valve; SP. septum primum; IVC, inferior vena cava; RA, right atrium; RAA, right atrial appendage.

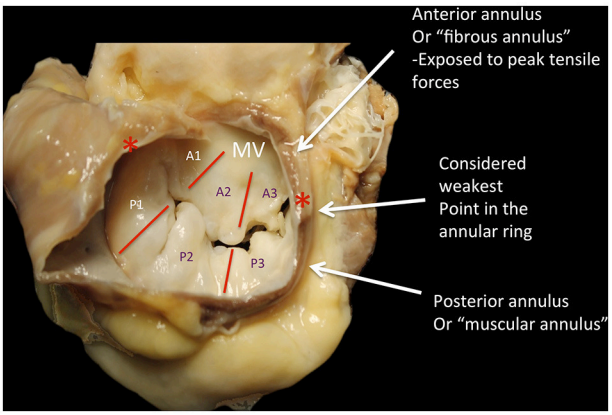

FIGURE 2 | The annulus fibrosus of the mitral is a discontinuous band of connective tissue that exists only in some parts of the attachment of the posterior leaflet, between the two fibrous trigones (red asterisks). The annulus does not exist at the attachment of the anterior leaflet, because the leaflet tissue is continuous with the aorto-mitral curtain that extends from the aortic valve annulus to the base of the anterior leaflet. During the diastole, the shape is grossy circular; during systole it has a saddle shape, with antero-septal diameter significantly smaller than the intercommissural diameter. The anterior leaflet is primarily related to the left ventricular outflow tract via the aorto-mitral curtain, whereas the posterior one is related to the muscular parietal base of the left ventricle. The systolic reduction of the mitral orifice is around 25%, due to the contraction of the base of the heart and the displacement of the aorto-mitral curtain toward the center of the orifice. P1-P3, posterior scallops of the mitral leaflet; A1-A3, anterior scallops; MV, mitral valve; Courtesy of Dr. M. Reisman, University of Washington.

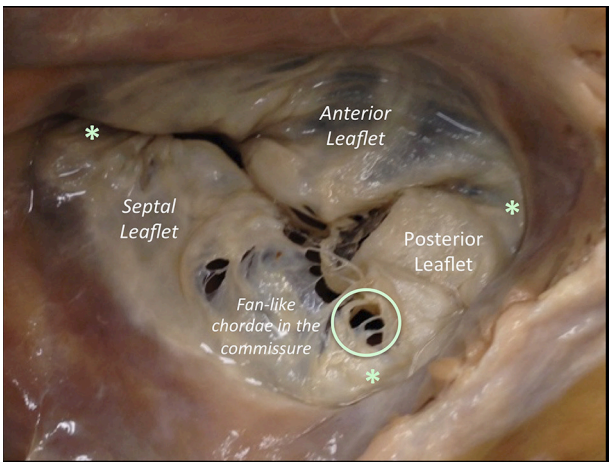

FIGURE 3 | The anterior leaflet of the TV is larger than the posterior, which is larger than the septal leaflet. The anterior leaflet is primarily attached to the right ventricular outflow tract, the posterior to the muscular wall of the right ventricle and the septal one to the septum. The anterior has a semicircular shape and likewise the MV, it is divided into an atrial zone, regular, and thin, and into a distal zone, the zone of coaptation, slightly irregular and thicker than the proximal one. In comparison to the MV, few chordae are attached to the ventricular side of the leaflet. The posterior leaflet, slightly smaller than the anterior is divided in the same proximal and coaptation zones. The septal leaflet is the smaller and less mobile, and roughly semicircular and likewise the other two leaflets, it has a proximal and a coapting zone. The commissures of the TV are three and separate the three leaflets (red asterisk). They are small semilunar leaflets, attaching on the annulus and with a free edge attaching characteristics fan-like chordae. There is one variable to take into account: in comparison to the left, the septal attachment of the TV is at a more apical level than the septal attachment of the MV. As a result, a portion of the membranous interventricular septum separates the LV from the right atrium (this anatomical feature explains left ventricular to right atrial shunts diagnosed in congenital malformations). This image has been adapted from Taramasso et al. (1).

Three anatomical structures close to the tricuspid annulus could be at risk of injury during interventional procedures:

(I) The non-coronary sinus of Valsalva, in particular the commissure between the non-coronary and the right coronary aortic cusp (especially in annuloplasty procedures);
(II) The bundle of His, which penetrates the central fibrous body and runs underneath the membranous septum 3–5 mm from the antero-septal commissure (the true landmark of His bundle) (**Figure 4**);
(III) The right coronary artery, the large single vessel coursing down the right AV groove and surrounding anteriorly the anterior TV leaflet.

Interventional Perspectives

The more anterior location of the TV compared to the MV (which is much more "TEE-friendly") makes intraprocedural TEE guidance particularly demanding in tricuspid procedure. In some circumstances, a combination of TEE, TTE and intracardiac echocardiography (ICE) is needed to obtain adequate imaging quality. The major interventional issue related to the TV compared to the MV is its larger orifice (**Figure 5**). If in normal conditions the TV area can already reach up to 9 cm^2, this area will be much larger in the presence of functional TR, representing more than 90% of TR etiology. In such a condition, the regurgitant orifice area is often bigger than 1 cm^2, i.e., more than double than in mitral position usually central and with a larger coaptation gap compared to MV. Therefore, a complete obliteration of the regurgitant area can be extremely cumbersome with the current repair devices. Similarly, it is easy to understand that also a replacement device has to be extremely big to cover the whole TV area. The large anatomy and the absence of annular calcifications are probably the two most important challenges to obtain sealing with a replacement device in TV position compared to the MV. The proximity of other cardiac structures has interventional implications in both mitral and tricuspid position. A peculiarity of the TV is the contiguity of the AV Node and His bundle (**Figure 4**), which is located in proximity of the septal TV annulus, close to the antero-septal commissure (the most common therapeutic target in MitraClip tricuspid procedures). In fact, an acute and complete AV Block (or even asystolia) can be induced just by the contact of any device with the His bundle, due to its compression.

Another important anatomical difference between MV and TV annuli from an interventional perspective is the different risk of coronary injury. The risk of coronary damage during interventional mitral or tricuspid procedures is mainly present in annuloplasty procedure (both direct and indirect), and it is

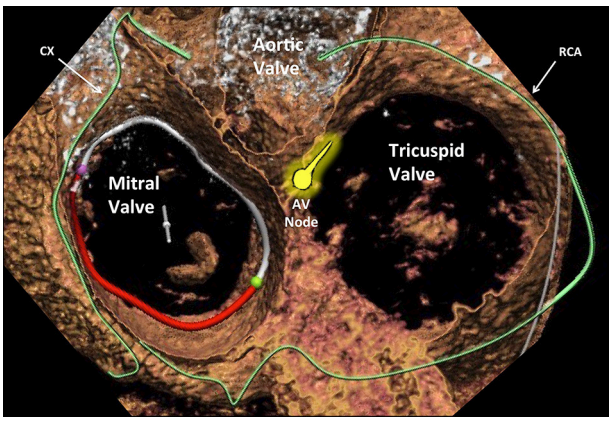

FIGURE 4 | Cross-sectional view of the three heart valves seen from above with atria removed. Advanced editing of a computed tomography image performed with 3mensio (Pie Medical Imaging, Netherlands) software. The proximity of the atrioventricular valves (different area can be appreciated) to the coronary arteries that are located in the atrioventricular groove (the circumflex for the mitral and the right coronary artery for the tricuspid) represents a similar aspect to be taken into account. Cx, circumflex artery; AVN, atrioventricular node; RCA, right coronary artery.

highly dependent on the coronary anatomy and dominance of the specific patients (**Figure 4**). Every therapy addressing the tricuspid annulus in a direct way, especially for unpractised operators, implies an augmented risk of damaging the right coronary artery.

VALVE LEAFLETS

Anatomical Description

The Mitral Leaflets

The MV comprises two leaflets, the anterior (or aortic) and the posterior (or mural), which are separated by two commissures (**Figures 2**, **5**) and without the septal attachment. The valve leaflets are segmented into six sections: from P1 to P3 for the posterior and from A1 to A3 for the anterior. This classification has been useful in describing morphology observed during surgical operation (6), multiplane 2D TEE echocardiography and 3D echocardiography (7).

The Tricuspid Leaflets

The TV comprises three leaflets: the anterior, the posterior and the septal, which are separated by three commissures. The septal leaflet is characteristic of the TV, with either direct chordal attachment to the septum or through the so-called Lancisi conal papillary muscle (PM). The TV leaflets are thinner, more translucent and more fragile compared to the MV (**Figures 3**, **6**).

Interventional Perspectives

Due to the different tissue property and characteristics, the chance of damaging or tearing the TV leaflets is higher compared to the MV. This has to be taken into consideration in case of leaflet repair, as MitraClip in tricuspid position.

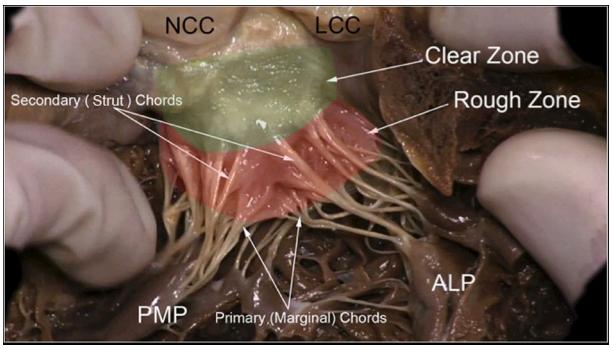

FIGURE 5 | The leaflets of the MV are clearly divided into two regions, the atrial zone which is at the base of the leaflets (green clear zone), thin and translucent, and the zone of coaptation, which is the distal rough and irregular zone (red rough zone), where numerous thick chordae origin and attach the leaflets to the PMs. Three types of chordae tendineae can be described: tertiary chordae which origin normally directly from the LV and are attached to the base of the posterior leaflets and commissure. The secondary chordae (Strut) extend directly from the PM and are attached to the body of the leaflets, ventricular side. The primary chordae (marginal), the most represented and robust, are attached to the free margin of the leaflets and the space between them is never more than 3 mm. The attachment to the free margin is normally bifurcated or trifurcated. When they are considered upon their position, it is possible to recognize one thick and resistant ≪ main chorda ≫ attached to the ventricular surface of the leaflet which forms with the opposite main chord a kind of arcade, supporting the center part of the leaflet. The commissural chordae, attached to the commissural tissue, are trifurcated giving them the characteristic fan-like appearance. PMP, posterior mitral papillary; ALP, anterior leaflet papillary; NCC, non-coronary cusp; LCC, left coronary cusp. Courtesy of Dr. M. Reisman, University of Washington.

SUBVALVULAR APPARATUS

The subvalvular apparatus of the MV and TV is similar and consists of two different structures with different characteristics: the papillary muscles (contractile function) and the chordae tendinae (elastic function).

Papillary Muscles

Mitral

The mitral PMs, which insert on the left ventricular (LV) free wall, are usually organized into two groups, which are the posteromedial and the anterolateral, situated just below the corresponding commissures (**Figure 7**). Not rarely, a third intermediate PM is found implanted between them, providing the chordae to A2 or P2 segments. Apical displacement of the posteromedial PM secondary to lateral myocardial infarction is the most frequent mechanism to underline asymmetrical tethering and functional MR post-infarction chronic ischemic heart disease.

Tricuspid

The tricuspid PMs are inserted on the right ventricular (RV) wall and usually organized into three groups: anterior, posterior and septal (**Figures 7**, **8**). The anterior PM is the dominant and is implanted on the anterior wall of the RV, near the

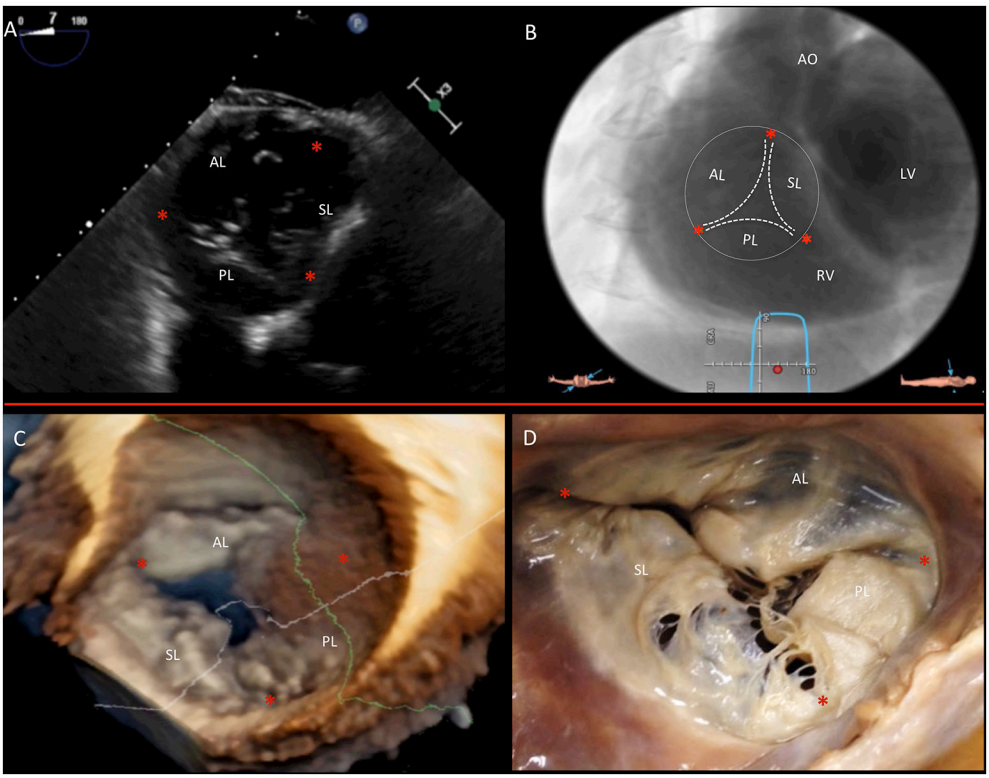

FIGURE 6 | Multimodality imaging of the TV. **(A)** Deep transgastric 2D TEE view, displaying the TV in short axis from the ventricular side. **(B)** Same en face view derived from MSCT angiography. **(C)** Short-axis atrial view of the TV on 3D TEE and during surgery **(D)**. Red asterisks are the commissures. AL, anterior leaflet; LV, left ventricle; PL, posterior leaflet; RV, right ventricle; SL, septal leaflet. This image has been adapted from Taramasso et al. (1).

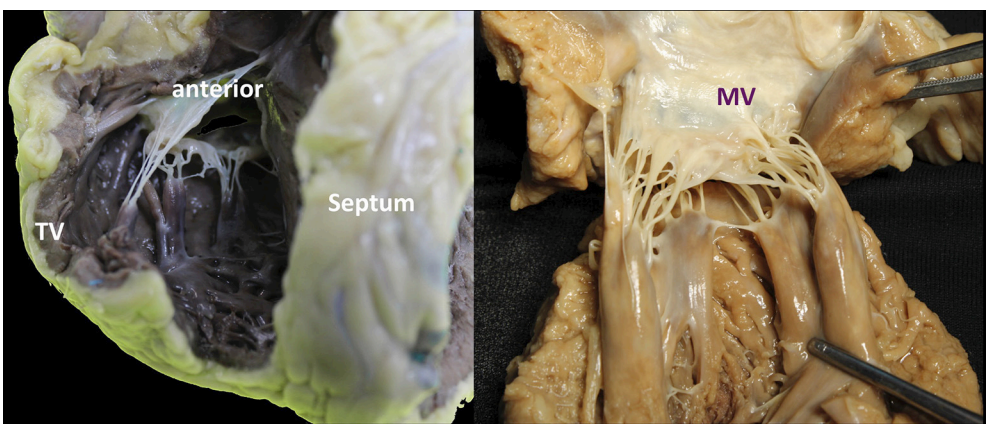

FIGURE 7 | Comparison of mitral and tricuspid PMs. **(A,B)** Each group of papillary muscles comprises either a single bulky papillary with multiple heads or otherwise several thinner papillary muscles from which arise the numerous chordae attaching to the leaflets. They are implanted on the muscular wall of the left ventricle at a junction situated ∼1/3 from the apex and 2/3 from the annulus. The position is varying little: the anterolateral PM is implanted at the junction between the septum and the posterior wall of the ventricle. The postero-medial PM is inserted on the lateral wall of the ventricle. The length of the PMs is variable, ranging from 2 to 5 cm. Importantly, no PMs attach to the left side of the ventricular septum.

apex, fusing with the moderator band. The chordae tendineae extend from the free margin to the PM. Three types can be described: the basal chordae (tertiary), the intermediary chordae (secondary) and the marginal chordae (primary), which are the most represented (8). Basically, having the TV three leaflets, with the posterior often divided in further scallops, it presents a more complex chordal structure in comparison to MV (9).

Interventional Perspectives

The main interventional issue related to the subvalvular apparatus is the risk of impingement of any device in the chordal apparatus, once the valve is crossed. Similarly in both MV and TV, the risk is higher in the commissural region, in which the density of chordae is the maximum, while the middle of the valve is chordae-free zone. This is particularly true for leaflet repair devices delivered antegrade, typically with the MitraClip.

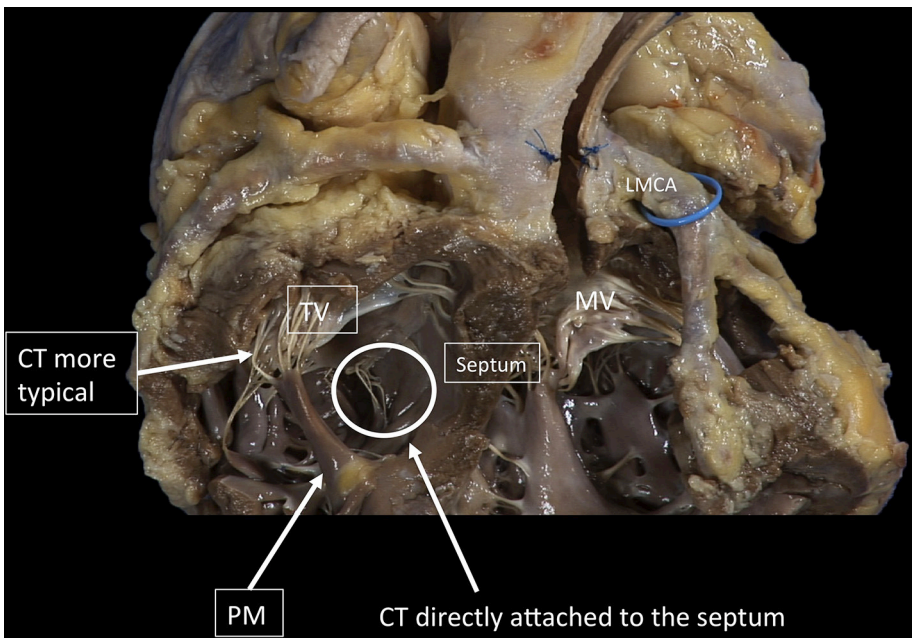

FIGURE 8 | The TV has a more complex chordal structure in comparison to MV. The chordae can be attached directly to the RV wall and septum, differently from the LV. On average, a number of 25 chordae inserts into the TV. The chordal system is hierarchical similar to the left one, dividing the types of chordae in basal, intermediary or secondary chordae and the marginal chordae, attaching to the free edges. The attachment of the marginal or primary chordae is usually single on the right, without bifurcating or trifurcating close to the edge and originating from various levels of the papillary muscles. Even if thinner, the chordae of the TV commissures are trifurcated with a characteristic fan-like disposition. CT, Chordae tendineae; PM, papillary muscle; MV, mitral valve; TV, tricuspid valve. LMCA, left main coronary artery (light blue circle). Courtesy of Dr. M. Reisman, University of Washington.

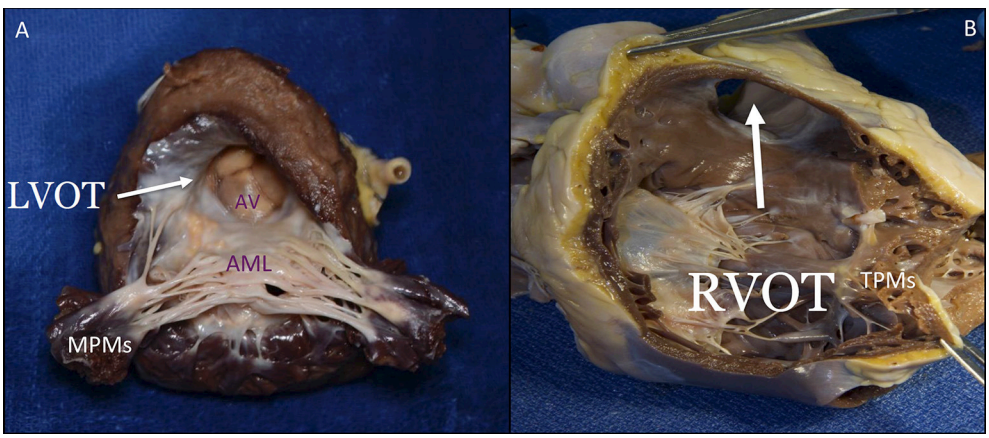

FIGURE 9 | The septal surface of the LV may be considered to have a sinus portion, most of which is trabeculated, and a smooth outlet (LVOT) portion **(A)**. The part of the sinus portion of the septum immediately beneath the mitral valve may be termed the inlet septum, and the rest of the sinus portion, the trabecular septum. The LVOT lies in front and to the right of the anterior mitral leaflet, corresponding to the inlet portion on the right ventricular side of the septum, and includes the atrioventricular septum. On the right side, the septal leaflet is the only one attached to the septum, but it leaves the RVOT free **(B)**. The lowermost of the small septal muscles attaches posterior to the trabecula septomarginalis and the uppermost, called the medial or conal PM (muscle of Lancisi), to the posterior limb of the septal band. The septal PM is almost not affected by tethering in case of RV dilatation. LVOT, left ventricular outflow tract; AV, aortic valve; AML, anterior mitral leaflet; MPMs, mitral papillary muscles; RVOT, right ventricular outflow tract; TPMs, tricuspid papillary muscles. This image has been adapted from Taramasso et al. (1).

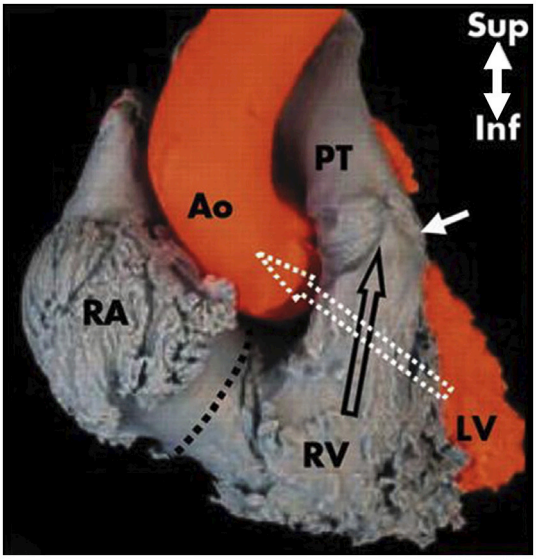

FIGURE 10 | The right outlet portion of the ventricular septum is smooth and has three components. The largest is the infundibular septum, which separates the pulmonary valve (with arrow) from the aortic and TV. A second part of the outlet portion of the septum is the anterior extension of the trabecular septomarginalis (septal band). A third small, very anterior portion is a narrow extension superior to the trabecular septum. The axes of the right and left ventricular outflow tracts differ significantly. That of the RV is almost vertically oriented, whereas that of the left ventricle angles sharply to the right, a characteristic criss-cross feature (white and black empty arrows), visible under fluoroscopy in the left anterior oblique projection and in the parasternal long axis view by two-dimensional echocardiography. RA, right atrium; Ao, Aorta; RV, right ventricle; PT, pulmonary trunk; LV, left ventricle. Modified from Ho et al. (12).

In presence of a commissural lesion, the risk of clip impingement is particularly high and can lead to impossibility to retrieve the device or chordal rupture with consequent worsening of the regurgitation. In TV the commissures are almost invariably the first therapeutic target (usually the antero-septal): a first clip is implanted close to the commissure, where the coaptation deficit is minimum, in order to approximate the leaflets, and may facilitate the implantation of further clips on the coaptation line. Since the only location that allows leaflet grasping is at the real commissure, risk of impingement or chordal injury is present in tricuspid clipping procedures. Similarly to the leaflet, also the chordal tissue of the TV is thinner and more fragile compared to MV, and this may increase the risk of damage, especially in case of multiple grasping attempts or in case of chordal impingement.

LEFT VENTRICLE, RIGHT VENTRICLE AND OUTFLOW TRACTS

Anatomical Description

Left Ventricle

The LV consists of a larger sinus portion, which supports the MV and includes the apex, and a much smaller outlet (outflow) portion beneath the aortic semilunar valve. Contrary to the RV, the inlet and outlet valves of the LV lie juxtaposed within its base, and inflow and outflow portions are separated by a curtain represented by the anterior MV leaflet (**Figure 9**). The LV trabeculations are characteristically fine compared with those in the RV (10).

Right Ventricle

The RV has a large sinus portion that surrounds and supports the TV (inlet portion) and includes the apex and an infundibulum (outlet portion) that supports the pulmonic valve. The inlet and outlet valves of the RV, opposite to the aortic and MV, are thus widely separated by the "Crista ventricularis" (11), minimizing any risk of right ventricular outflow tract obstruction (RVOT). The entire sinus portion of the RV and most of the infundibulum (both free wall and septum) are coarsely trabeculated (12). The conduction system (bundle of His) perforates the central fibrous body closer to the RV side, therefore the possibility to damage this structure from the left, in comparison to the right side (**Figure 10**), is very remote.

Interventional Perspectives

The close relationship between the anterior mitral leaflet, the aortic valve and the left ventricular outflow tract (LVOT) has important consequences: the implantation of a transcatheter heart valve inside the native or repaired MV forces the anterior leaflet in an "open position," that may encroach on the LVOT. This septal displacement of the anterior mitral leaflet is exaggerated when the aortic and mitral annular planes are acutely angulated, when the interventricular septum is hypertrophic and bulges toward the LVOT, in presence of an elongated leaflet, and when the valve implant extends or flares into the LV. On the contrary, the marked separation between the TV and the pulmonary valve by the Crista supraventricularis and the wide-open angle between them make the risk of RVOT obstruction really low with any type of tricuspid device, in any anatomical context (**Figures 9**, **10**). While transapical LV access is frequently used for aortic and MV procedures, apical RV access presents several issues. The thin and trabeculated RV wall makes this approach potentially risky, especially in the context of RV dilatation and dysfunction associated to functional TR.

CONCLUSIONS

With the fast development of transcatheter TV therapies, physicians are facing up with a new challenging anatomical scenario. A deep understanding of the anatomy of the TV and of the right heart chambers, and their differences compared to the left-heart, is fundamental to improve safety and efficacy. The specific anatomical features of the TV, the low quality of intraprocedural TEE guidance and the absence of a standardized nomenclature remain major open issues to be addressed in TV intervention.

AUTHOR CONTRIBUTIONS

AP and MT wrote the manuscript. MZ, MR, and FM supervised, contributed with specific iconography and revised critically the paper.

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OPINION
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Transcatheter Treatment of Tricuspid Valve Disease: An Unmet Need? The Surgical Point of View

David C. Reineke, Eva Roost, Florian Schoenhoff, Miralem Pasic, Alex Kadner, Lars Englberger and Thierry P. Carrel*

Department of Cardiovascular Surgery, University Hospital Bern, Bern, Switzerland

Keywords: tricuspid valve insufficiency, interventional therapy, surgery, new devices, future strategy

INTRODUCTION

Tricuspid valve disease can either be stenotic or regurgitant. While stenotic lesions are very rare and mainly caused by rheumatic fever or carcinoid disease, the most common disease of the tricuspid valve is regurgitation (1). As with all valves, primary and secondary entities exist. This opinion paper will focus on the most frequent pathology, the functional tricuspid regurgitation (FTR), which primarily is considered as disease of the right ventricle.

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Edited by:
Maurizio Taramasso, UniversitätsSpital Zürich, Switzerland

Reviewed by:
Luigi Biasco, Cardiocentro Ticino, Switzerland
Benedetto Del Forno, San Raffaele Hospital (IRCCS), Italy

****Correspondence:***
David C. Reineke
david.reineke@insel.ch

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WHY DO WE TALK ABOUT THE FORGOTTEN VALVE?

Most editorials on the tricuspid valve speak about "the forgotten or untreated valve." Why is that so?

In our view, four facts are responsible for this development:

1. In the early seventies right sided endocarditis due to intravenous drug abuse was treated simply by surgically removing the valve, leaving behind torrential tricuspid regurgitation (TR). This was supported surprisingly well. Long-term data was of course scarce due to this selected patient population.
2. Initially it was believed that left-sided valve surgery would resolve the problem of the tricuspid valve. TR was generally thought to be a bystander with the main focus on the correction of left sided pathology. However it has been shown that TR does not resolve following left-sided heart surgery with relevant influence on long-term survival.
3. For a long time the focus was put on TR alone. Data has shown that not only the presence of TR represents a significant risk factor for severe TR during follow-up after mitral valve surgery, but that annular dilatation alone is a predictive factor for later TR.
4. In the pioneering days of heart surgery it was all about survival and TR was never demonstrated to adversely influence early outcome. This observation applied for the whole complex of right sided pathologies which only become relevant as patients' survival of left sided heart disease has considerably improved. A similar development can be seen in patients suffering from chronic pulmonary embolic disease. Right heart disease is just not as "appealing" as left heart disease.

WHAT DO THE GUIDELINES TELL US?

Guidelines supported this scientific and practical deficit on therapy for several decades. While American and European guidelines where relatively fast in listing a class I indication to perform tricuspid valve repair for severe TR in patients who are undergoing mitral valve (MV) surgery

both guidelines where for a long period quite silent about performing concomitant tricuspid valve surgery for coronary bypass, aortic valve replacement or other cardiac surgery (2, 3).

The ESC Guidelines also listed tricuspid surgery as a Class I indication in the case of severe primary TR (or tricuspid stenosis) with symptoms and without severe RV dysfunction (3). The US guidelines on the other hand only listed this scenario as "reasonable" and as class IIa indication (2). This is one of the rare exceptions where valve disease with symptoms is not listed as a Class I indication for surgery in the guidelines (2) and reflects the general reluctance to operate on some of these patients who have already developed irreversible right ventricular (RV) dysfunction.

Patients with FTR remain asymptomatic for a long time despite considerably impaired right ventricular function (4). As a result the population with a potential indication to treat TR is of advanced age, has often already had cardiac surgery and suffers from extensive RV dysfunction. This is actually a shame as surgery performed in early stages of the disease is relatively easy and a straight forward procedure with very acceptable operative risk (5).

FORGOTTEN OR JUST UNNOTICED?

Despite talk of the "forgotten valve," already 20 years ago, renowned specialists in the field had the following messages which went unnoticed (5, 6):

- Tricuspid annular dilatation is more reliable than regurgitation and represents a more consistent landmark.
- TR alone is a unreliable parameter as it very much depends on several factors like volume status, preload, afterload and right ventricular dysfunction.
- TR is a continuing process, worsening despite treatment of left-sided pathologies. Already then the group around Gilles Dreyfus were able to show progression of the disease in 30% of patients during a follow-up between 5 and 15 years.

Treating annular dilatation beyond a given size improves functional status and there is a clear trend toward better survival compared to patients who did not receive treatment.

This concept is supported by several groups including the American College of Cardiology/American Heart Association guidelines who included a type IIa recommendation for patients with a threshold diameter of 40 mm (7–13).

The need of treatment of this polymorbid patient population has resulted in the development of a variety of interventional devices. But, it becomes evident that while we are again able to quite effectively treat left sided pathologies with TAVI and mitral devices, right-sided therapy options still stay far behind.

In the current ESC/ECTS guidelines with updated indications for the evaluation and surgical intervention in patients with TR, interventional strategies have only found their place in the chapter "Gaps in evidence": "The potential role of transcatheter tricuspid valve treatment in high-risk patients needs to be determined (14)."

Sadly, the updated guidelines don't consider the tricuspid valve regurgitation as a general consequence of left sided heart disease but again have the tendency to stress the importance of the awareness of tricuspid disease in patients with significant mitral valve disease following data acquired after mitral clip therapy. In contrast, recent literature demonstrates that even after TAVI tricuspid valve dysfunction is associated with significantly increased mortality. This underlines that left-sided heart disease in general is responsible for FTR (15).

PATHOPHYSIOLOGIC BACKGROUND

From a morphological standpoint FTR is known for its dynamic disease progression and can be divided into three phases (16):

1. Dilatation of the RV results in dilatation of the tricuspid annulus. At this stage TR might not even be present depending on the degree of annular dilatation and lack of leaflet coaptation.
2. Progressive dilatation of the RV and tricuspid annulus will lead to severe lack of coaptation resulting in significant TR.
3. RV dilatation especially in the region of the free wall will in addition to annular dilatation lead to tethering of the tricuspid leaflets, due to the attachment of the papillary muscles of the tricuspid leaflets to the free wall of the RV. A tethering height of more than 8 mm is reported to be predictive of more than moderate functional TR.

SURGICAL APPROACHES

According to these three phases, surgical repair of the tricuspid valve for functional TR requires tailored strategies.

In the first two stages, tricuspid annuloplasty alone gives excellent results. The third phase however necessitates treatment of the annular dilatation as well as the leaflet tethering since annuloplasty alone is unlikely to be successful in treating TR. Here two options come into play—a reconstructive approach or the replacement of the valve.

A variety of supplemental techniques for addressing leaflet tethering, such as anterior leaflet patch augmentation, double-orifice valve or bicuspidization repair, have demonstrated efficient and lasting results. Not least, these techniques provide the concept and justification for many proposed catheter-interventional approaches. Regarding the replacement of the valve, a potential recurrence of TR due to disease progression is prevented (16). However, life-long and rather aggressive anticoagulation therapy after mechanical valve implantation or the inevitable long-term valve degeneration following implantation of a biological prosthesis present significant drawbacks. With the arrival of interventional valve-in-valve technology, the choice for a biological prosthesis appears to be preferable.

INTERVENTIONAL APPROACHES

Transcatheter tricuspid valve intervention (TTVI) is at an early stage of introduction into practice and only a few hundred patients have been treated so far (17, 18). The first interventional valve replacement was very recently performed (19).

According to their mode of action tricuspid valve catheter devices can be divided into four groups (20):

- Tricuspid valve annuloplasty devices
- Tricuspid edge-to-edge technique
- Heterotopic caval valve devices
- Coaptation devices

Due to the nature of the disease progression, the majority of patients qualifying for interventional treatment are usually those with advanced disease (phase two to three). According to extensive research done on surgically treated patients, most of the above mentioned interventional devices will not be effective in treating the pathology. It is our strong opinion, that industry and doctors should concentrate on annuloplasty devices and devices replacing the tricuspid valve. It would be unwise to flood the market with devices not able to treat the most common pathology and by that depriving very sick patients from an effective therapy.

CONCLUSION

In conclusion, there is a clearly unmet need for the interventional treatment of TR mainly in very sick patients with FTR. Nonetheless device development and introduction must focus more on the mechanism of the disease in order to effectively treat it. The focus needs to be on annuloplasty devices and complete valve replacement strategies. One can only hope, that the current interest into interventional therapy of the tricuspid valve disease will bring back the "forgotten valve" into the conscience of the cardiological and surgical community. On the one hand, reminding cardiologists, that beside asymptomatic presentation of their patients a timely referral is mandatory for allowing a low-risk and optimal surgical intervention, on the other hand, reminding surgeons to address more consequently concomitant tricuspid valve disease and to apply repair strategies. The availability of interventional catheter-based techniques must not serve as an excuse for again "forgetting" the dysfunctional tricuspid valve and delaying therapy.

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REVIEW
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Surgical Techniques for Tricuspid Valve Disease

Igor Belluschi, Benedetto Del Forno, Elisabetta Lapenna, Teodora Nisi, Giuseppe Iaci, David Ferrara, Alessandro Castiglioni, Ottavio Alfieri and Michele De Bonis*

Department of Cardiac Surgery, IRCCS San Raffaele University Hospital, Milan, Italy

Tricuspid valve disease affects millions of patients worldwide. It has always been considered less relevant than the left-side valves of the heart, but this "forgotten valve" still represents a great challenge for the cardiac surgeons, especially in the most difficult symptomatic scenarios. In this review we analyze the wide spectrum of surgical techniques for the treatment of a diseased tricuspid valve.

Keywords: tricuspid, valve, surgery, techniques, disease

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Edited by:
Maurizio Taramasso, UniversitätsSpital Zürich, Switzerland

Reviewed by:
David Chistian Reineke, Clinic for Cardiovascular Surgery, Inselspital, Switzerland
Alexander Lauten, Charité Universitätsmedizin Berlin, Germany

****Correspondence:***
Benedetto Del Forno
delforno.benedetto@hsr.it

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INTRODUCTION

The disease of TV generally appears in the form of regurgitation. Secondary or functional disease represents the more suitable case for a repair, while the organic or primary deterioration of the valve is unlikely to be repaired. Over the past four decades, many procedures have been described, varying from simple sutures to a large number of prosthetic rings. The present evidence reports a superiority of the repair over replacement, in particular when annuloplasty is associated. Here we summarize the most commonly used techniques to repair this forgotten valve or replace it in the worst cases.

TRICUSPID VALVE REPAIR TECHNIQUES

Functional Disease

When pulmonary hypertension develops as a consequence of a left-heart pathology, a functional tricuspid regurgitation may appear. In this case the valve is not affected by organic lesions, nevertheless an annular dilatation may be associated.

Current guidelines suggest treating this disease when the regurgitation becomes severe and only if a left-heart surgery is planned. If the grade of insufficiency is less than severe, surgery should be performed in case of a septal-anterior diameter $\geq$ 40 mm (or $\geq$21 mm/m^2). If there are signs of progressive right ventricle dysfunction or dilatation (in the absence of left or right ventricle severe decline or pulmonary hypertension), even if in asymptomatic patients, a reintervention for tricuspid regurgitation is needed after a previous left-side surgery (1).

The key of the tricuspid valve repair consists of the reduction in the right ventricle after-load and in the annulus diameter (2).

Suture Annuloplasty

Kay procedure

In 1965 Kay et al. described, for the first time, a repair technique to treat secondary tricuspid regurgitation. Using a 1-0 silk suture (placed through the posterior leaflet and the commissures), the posterior leaflet is completely excluded, and a functional bicuspid valve is finally obtained. It is preferable to put other sutures to reinforce the first stitch. In addition, some variants (i.e., the positioning of some pledgets) could be performed (**Figure 1A**).

De Vega procedure

The De Vega annuloplasty has been proposed in 1972. This procedure consists of reducing the area of the tricuspid annulus and rapidly became the most popular technique for the treatment of annular dilatation. It is generally performed by two 2-0 Ti-cron or 4-0 polypropylene running parallel sutures (with 5–6 mm bites), starting on the postero-septal commissure, through the endocardium, and directed around the perimeter of the orifice in a counterclockwise direction reaching the antero-septal commissure. The other parallel suture is placed about 1–2 mm outside the previous one, and finally tied together (**Figure 1B**) (4). In case of fragile endothelium, the sutures could cut the annulus, therefore some pledgets may be positioned between every bite to reinforce the annuloplasty as proposed by Antunes and Girdwood in 1983 (5).

Ring Annuloplasty

The idea of a prosthetic ring to reinforce the tricuspid annulus was first introduced by Carpentier in 1971. Rigid or semi-rigid ring has been designed to fix the annulus during systole, restoring the physiologic geometry of the valve, while flexible ones may be used as well to reduce the annular dilatation, but failed to restore the 3D morphology (6, 7). The right size of the ring is chosen by measuring the distance from the antero-septal to postero-septal commissures (i.e., the surface of the anterior leaflet) and the ring is then implanted using eight to ten 2-0 Ti-cron stitches starting posteriorly (at the midpoint of the septal leaflet) and then proceeding counterclockwise. The surgeon must pay attention during the placement of stitches to damage the conduction system and to avoid the aortic root at the level of septal and anterior leaflet, respectively. The last stitch is placed above the antero-septal commissure, and the ring is finally parachuted and fixed (**Figure 2**).

Enlargement of the Anterior Leaflet

Sometimes, an isolated annuloplasty is not sufficient to correct the disease, especially in case of severe tethering. As a consequence, in 2008 Dreyfus et al. proposed the enlargement of the anterior leaflet to solve this problem. After removing the native anterior leaflet, a piece of autologous pericardium is prepared by measuring the length as the distance between the antero-septal and the antero-posterior commissures, whereas the height as the greatest distance between the detached leaflet and the annulus. Finally, the patch is sutured with a polypropylene 5-0 suture to the annulus and a semi-rigid annuloplasty ring is implanted (8).

"Clover Technique"

In 2003 Alfieri et al. presented a technique for the correction of severe functional tricuspid insufficiency in case of important tethering. It consists of stitching together the middle point of the free edges of the tricuspid leaflets by using a 5.0 polipropylene suture without pledgets and adding a semi-rigid ring. At this point, the valve became clover-shaped, so this technique has been called "the Clover Technique." It was first introduced for the treatment of post-traumatic tricuspid regurgitation, while later became effective even in complex cases both of primary or secondary tricuspid regurgitation (9) (**Figure 3**).

Results

The failure rate for the treatment of tricuspid valve by using a suture or a ring annuloplasty at one month after surgery ranges from 8 to 15% (10, 11). Risk factors include: the severity of preoperative tricuspid regurgitation, presence of pacemakers, pulmonary hypertension, LV dysfunction, increased left ventricular remodeling, severe tethering of the tricuspid leaflets and the use of suture rather than ring annuloplasty. Nevertheless, many observational studies and RCTs compared the two types of annuloplasty (suture or ring): the conclusion was that the placement of a ring is associated with a more durable repair, especially when severe tricuspid annular dilation or pulmonary hypertension are present (12, 13). In addition, when compared to suture annuloplasty, tricuspid rings also provide better long-term and event-free survival up to 15 years

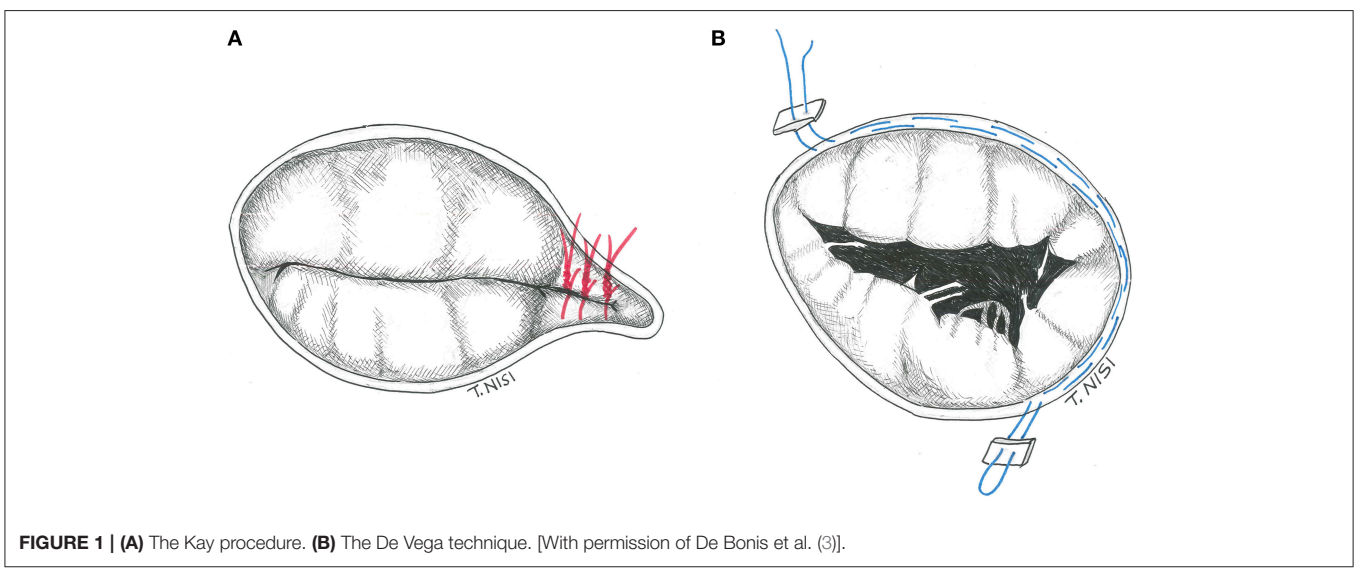

FIGURE 1 | (A) The Kay procedure. **(B)** The De Vega technique. [With permission of De Bonis et al. (3)].

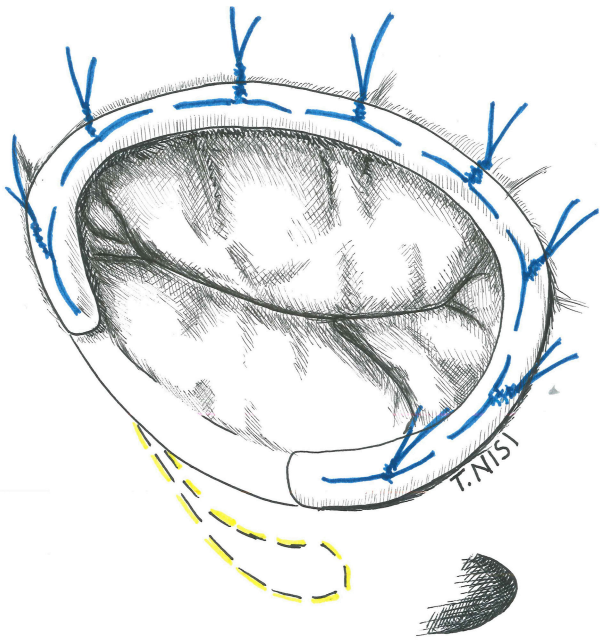

FIGURE 2 | The image shows a tricuspid ring annuloplasty. [With permission of De Bonis et al. (3)].

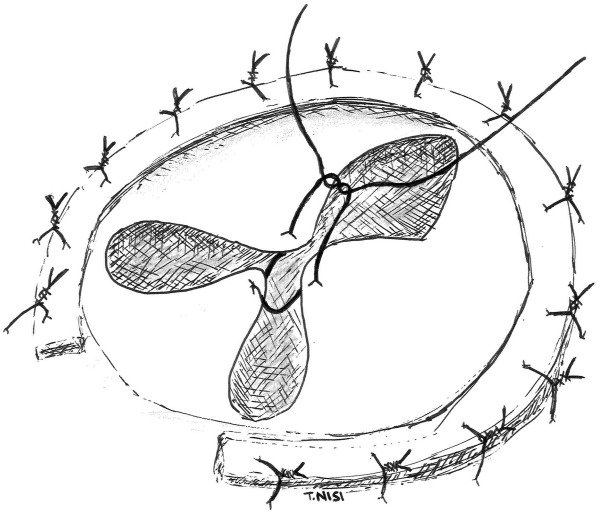

FIGURE 3 | In this picture the "Clover Technique" by Alfieri et al. is reported. The leaflets are joined together, and the valve finally assumes a shape like a clover. [With permission of De Bonis et al. (3)].

after surgery (14, 15). In case of severe tethering associated to annular dilatation, annuloplasty alone is unlikely to be durable (16) so an additional procedure, such as the enlargement of the anterior leaflet or "clover technique," may be used to obtain a more durable repair (8, 9). However, more studies are mandatory to prove the long-term outcome of these procedures.

Tricuspid Valve Repair for Primary Disease

The organic disease of the tricuspid valve (i.e., primary insufficiency) is most commonly caused by degenerative valve disease or bacterial endocarditis (generally in western countries), while rheumatic disease still remains the most prevalent form in developing countries.

Leaflet lesions may include: excess of tissue, thickening, perforation and tear; whereas the chordae tendinae and the papillary muscles may be fused (especially in the rheumatic disease), elongated or damaged. Restoring the normal leaflet mobility, ensuring an adequate surface of coaptation, is the aim of the techniques reported, always followed by ring annuloplasty.

Intervention on the Leaflets

If the prolapsing segment is less than one tenth of the leaflet surface area and the chordal rupture is small, a triangular resection can be performed. After resection, a 5-0 polypropylene running suture or interrupted stitches are used for the leaflet synthesis. An annular plication and/or a pericardial patch may be used in case of endocarditis (**Figure 4**).

Intervention on the Chordae

In case of important chordal rupture both chordal transposition and artificial chordae implantation may be adopted, as for the mitral valve repair. In the first case, a small segment of adjacent non-prolapsing leaflet is resected and then implanted on the prolapsing one using 5-0 polypropylene running suture.

Otherwise, for the implantation of artificial chordae, an accurate measurement of native chordae of a non-prolapsing leaflet is performed and used to choose the proper length. Then the neo-chordae are implanted on the corresponding papillary muscle and finally on the free margin of the prolapsing leaflet.

Intervention on the Papillary Muscles

A sliding papillary muscle plasty technique may be the best choice to correct a diseased papillary muscles or extensive chordal elongation. The elongated papillary muscle, or the papillary muscle underlying the elongated chordae, is lowered to the proper level and fixed to the adjacent one using 5-0 polypropylene interrupted stitches.

Intervention on the Commissures

When the rheumatic disease is present, it may provoke a fusion of the three commissures (generally associated with that of the underlying chordae). The surgical technique consists of performing commissurotomy and dividing fused chordae using an 11 blade under direct visualization.

TRICUSPID VALVE REPLACEMENT

Sometimes the valve structure is dramatically compromised (such as in endocarditis, carcinoid syndrome, and radiation induced disorder), therefore reconstructive procedures may result not adequate and the decision for tricuspid valve replacement should be taken. Even in extreme dilatation due to functional tricuspid regurgitation, valve replacement should be

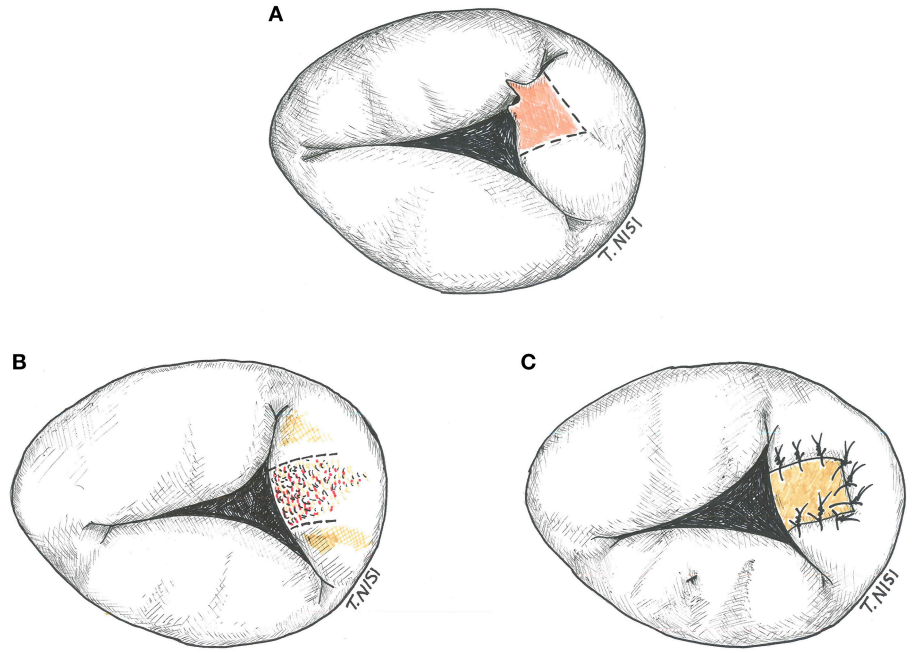

FIGURE 4 | (A) Tricuspid triangular resection. **(B)** Resection of the leaflet in a case of bacterial endocarditis. **(C)** The gap is restored by using an autologous pericardium patch. [With permission of De Bonis et al. (3)].

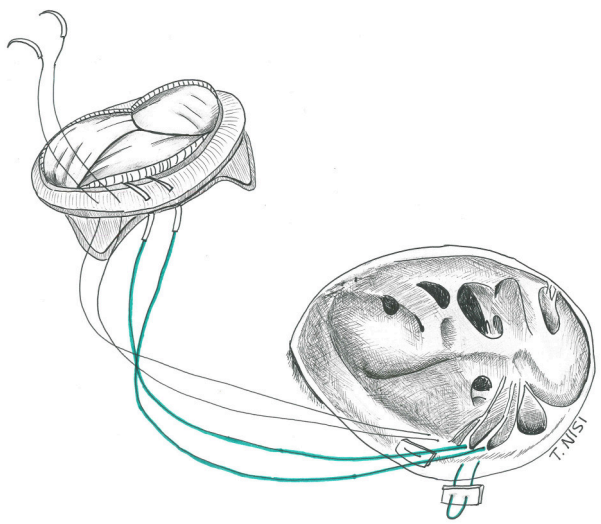

FIGURE 5 | Tricuspid valve replacement using a bio-prosthesis. [With permission of De Bonis et al. (3)].

considered. The choice of using a cardioplegic heart arrest or a beating heart procedure depends on the surgeon's preference and the risk of the patients, but sometimes combined techniques are used as well.

Choice of the Prosthetic Valve

The choice of the prosthesis type (whether biological or a mechanical) should follow the same algorithm used for other cardiac valves (i.e., age, pathology, comorbidities etc.). By the way, the surgeon must remember that the specific right-heart low-pressure chambers and lower level of prostacyclin (a powerful inhibitor of platelet aggregation) may increase the risk of valve thrombosis (17, 18).

Furthermore, the mechanical choice could be prohibitive for a future pacemaker need. Given that, biological prostheses would seem to be an ideal solution. In addition, reoperations rate after bio-prosthetic tricuspid valve replacement seems to be lower compared to bio-prosthetic mitral valve replacements, and this may be due to the lower pressure and to the limited life expectancy in TVR patients (19). On the other hand, other studies reported similar survival rates (20–22). Finally, mechanical valve thrombosis is rarely fatal and often is successfully treated increasing anticoagulation therapy or using thrombolysis (23). However, in case of small size—and/or OAT—patients, the mechanical choice could be preferred (24).

It is not possible to state that there is a "gold standard" for prosthetic selection in tricuspid valve replacement. As a consequence, this choice should be strictly tailored considering the patients' profile (i.e., young patients < 40 y.o. may benefit a mechanical TVR).

Surgical Technique

The native leaflets are generally resected (or fenestrated after the TVR in case of RVOT obstruction), leaving a 2 to 3 mm fringe of tissue on the annulus, dividing the chordal attachments deep in the right ventricle and keeping the septal leaflet *in situ*. Then the suture is performed using an everting 2-0 or 3-0 pledgeted Ti-cron stitch, along the circumference of the annulus from the atrial

to the ventricular side of the valve, starting at the anterior leaflet and proceeding clockwise. Alternatively, when there is a need for a quicker procedure, pledgets sutures are used only at the level of the septal leaflet, while two continuous 2-0 Ti-cron sutures are used for the remaining circumference of the valve. An accurate sizing is crucial to avoid obstruction and septal lesions. The bioprosthetic valve must be properly oriented to avoid obstruction of the right ventricle outflow tract considering its stent posts (which should stay at the 12, 4, and 8 o'clock positions). After passing the sutures through the sewing ring and slipping down the prosthesis, the sutures are finally secured starting from the septal leaflet (**Figure 5**).

Results

The sub-optimal results of tricuspid valve replacement have always represented a difficult argument in cardiac surgery. As reported in many series, the replacement of tricuspid valve is generally adopted in reoperations, which represents itself an adjunctive intrinsic operative risk (20, 25). Some studies showed an operative mortality of 18%. NYHA class, female gender, bilirubin level, preoperative diuretic dose and preoperative hemoglobin level are all associated with increased operative mortality (25, 26). Late referral is the main issue in the management of these patients: the presence of enlarged and dysfunctioning right ventricles severely conditioned the operative results. The choice of a beating-heart technique without the need of aortic cross-clamping, generally in redo cases, represents an optimal tool and has showed acceptable acute mortality, especially if performed in the absence of ascites, significant right ventricular dysfunction and pulmonary hypertension (27). Regarding the outcomes on long-term, they are acceptable considering the clinical conditions of these patients. However, the presence of risk factors such as pulmonary hypertension, age at intervention and redo surgery, seem to have an impact on survival at follow- up (26, 27).

CONCLUSION

This review provides an overview of the surgical techniques for the treatment of functional and organic tricuspid regurgitation. When possible, valve repair still remains the most useful procedure, while replacement is generally preferred in the most demanding cases. Surgeons must know the wide spectrum of this surgical techniques. Only the accurate choice of the most appropriate procedure will provide optimal and long-term results.

AUTHOR CONTRIBUTIONS

BD and IB: equally draft the manuscript; TN: drawn the anatomical pictures; GI and DF: reviewed the manuscript; EL, AC, OA, and MD: supervised the manuscript.

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REVIEW
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Transcatheter Tricuspid Valve Replacement: Principles and Design

Ozan M. Demir[1,2†], Damiano Regazzoli[1†], Antonio Mangieri[1], Marco B. Ancona[1], Satoru Mitomo[1], Giora Weisz[3], Antonio Colombo[1] and Azeem Latib[1,4]*

[1] Interventional Cardiology Unit, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy, [2] Department of Cardiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom, [3] Department of Cardiology, Montefiore Medical Center, New York, NY, United States, [4] Division of Cardiology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Tricuspid regurgitation (TR) may affect as much as 65–85% of the population with the prevalence of moderate-to-severe TR in the United States reported at greater than 1.6 million. However, only 8,000 tricuspid valve operations are performed annually in the United States. As severe TR is associated with poor outcomes, there is an unmet clinical need for surgical or percutaneous transcatheter based treatment of TR. Over the last two decades there have been significant developments in percutaneous transcatheter based therapies for valvular disease. However, this progress has not been mirrored for the tricuspid valve until recently; we are now at a cross-roads of new transcatheter devices becoming available for treatment of TR. In this review, we discuss the principles of performing transcatheter tricuspid valve replacement, analyze the devices that can be utilized and outline the challenges related to this procedure.

Keywords: tricuspid regurgitation, valve replacement, cardiac imaging, tricuspid valve, structural heart disease

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****Correspondence:***
Azeem Latib
alatib@gmail.com

† These authors have contributed equally to this work as first authors

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INTRODUCTION

Tricuspid regurgitation (TR) is a commonly encountered manifestation of valvular heart disease, it may affect as much as 65–85% of the population (1, 2). The majority of these are no more than mild TR which is deemed non-pathological and a normal variant, however, moderate-to-severe TR is usually pathological and associated with poor prognosis (3). The etiology of TR can be divided into primary (organic) and secondary (functional), in relation to the presence of structural abnormalities of the tricuspid valve (TV) apparatus. Approximately 80% of significant TR is functional (FTR), occurring due to annular dilation and subsequent leaflet tethering causing malcoaptation (4, 5). Organic TR can be either congenital or acquired. Congenital primary TR may arise due to Ebstein's anomaly, atrioventricular defects and myxomatous prolapse. Acquired primary TR can occur due to endocarditis, rheumatic disease, carcinoid, flail leaflets caused by trauma, or from pacemaker lead implantation (6). Patients with TR often experience clinical symptoms of right-sided heart failure, including dyspnea, restriction of functional capacity, frequent hospitalization, liver, and kidney failure.

The prevalence of moderate-to-severe TR in the United States has been reported at greater than 1. 6 million. Despite this only 8,000 TV operations are performed annually in the United States (7). Furthermore, with increasing severity of TR, 1-year mortality increases, reaching greater than 36% in those with severe TR (3). Hence, there is an unmet clinical need for surgical or percutaneous treatment of TR. Over the last two decades, there has been significant developments in transcatheter based therapies for valvular disease. However, this progress has not been mirrored for the TV

until recently; we are now at a cross-roads of new transcatheter devices becoming available for treatment of TR. In this review, we discuss the principles of performing transcatheter tricuspid valve replacement (TTVR), analyze the devices that can be utilized and outline the challenges related to this procedure.

PRINCIPLES OF TRANSCATHETER TRICUSPID VALVE REPLACEMENT

The development of devices specifically designed for percutaneous TV repair or replacement are currently at an early stage. In this section, we will analyze the main challenges of TTVR procedures, in order to become a safe and effective alternative to medical therapy or high-risk surgical interventions.

Tricuspid Valve Anatomy and Technical Challenges

The TV apparatus is a complex structure consisting of 3 leaflets (anterior, posterior and septal) that are inserted to the tricuspid annulus and attached through the chordae tendinae to the papillary muscles of the right ventricle (RV). The tricuspid annulus is relatively less fibrous when compared with the mitral valve and the right coronary artery surrounds the parietal attachment of the valve. The normal physiological valve is a dynamic, nonplanar structure that varies in size and shape throughout the cardiac cycle (8).

This anatomical and functional complexity reflects on different procedural issues that must be taken in account during the development of tricuspid prosthesis and relative delivery systems (**Figure 1**):

- *Access selection:* One of the main anatomical challenges for current generation TTVR devices is the dimensions of the TV annulus; the TV annulus is large (larger than mitral) and it gets even larger when longstanding FTR and RV dilation are present. Hence, prosthetic TV valves have a large profile requiring large caliber sheaths. Large bore venous access (up to 45 Fr, with current devices) is of paramount importance when planning a replacement procedure and led to the preferential selection of three potential sites, that have potential advantages and disadvantages (9). Trans-jugular access, obtained either percutaneously or surgically, offers a good angle to approach the TV, with a delivery system that requires less steering, but requires a vein large enough to accommodate the sheath without being damaged. The femoral vein is the safest access route due to its size, but the angle between the inferior vena cava and TV is steep and may hamper the procedure. Trans-atrial approach requires a surgical approach (anterior right thoracotomy) but allows direct management of the access site. There is no clear answer on which of these is the better access route, although a percutaneous route will be essential for success.
- *Valve anchoring:* The tricuspid annulus is not calcific, is a three dimensional and dynamic structure; therefore, the possibility to achieve good prosthesis fixation and stability is a major issue. While no clear data is currently available, it can be hypothesized that a large prosthesis in tricuspid position may need a great capability of adaptation to the aforementioned anatomical characteristics: self-expanding devices may be more effective and with lower risk of annular stretching and damage. On the other hand, the TV prosthesis is associated with a lower risk of outflow tract obstruction as compared with mitral valve and active grasping of the native tricuspid leaflets may be not needed (10). However, at present valve anchoring is still a major unanswered issue.
- *Interaction with conduction system and with pacing devices:* The atrioventricular (AV) node lies in the muscular portion of the atrio-ventricular septum, near the ostium of the coronary sinus (at the apex of the triangle of Koch). The bundle of His is a direct continuation of the AV node and it passes through the right trigone of the central fibrous body to reach the ventricular septum. This area is near to the commissure between septal and anterior tricuspid leaflets (11). This close relationship between the tricuspid structure and the conduction system may be an issue when planning TTVR. In fact, surgical annuloplasty with dedicated tricuspid rings is often incomplete in order to avoid placing stitches in the septal area to reduce the incidence of complete AV block and subsequent pacemaker implantation. Percutaneously implanted bioprosthesis will likely not be able to avoid stretching that area. The incidence of rhythm disturbances is therefore expected to be higher than with repair, eventually leading to a second major issue: how to manage pacemaker devices during valve implantation. Indeed, prosthesis deployment may lead to a dislodgment of a pre-existing ventricular lead and, on the other hand, the prosthesis itself may hamper PM implantation.
- *Antithrombotic regimen:* No evidence is available on the selection of antithrombotic regimen specifically following TTVR (12). However, considering the low flow on the right-side of the heart and the size of the TTVR prosthesis, we would recommend life-long anticoagulant therapy in all patients with many patients already having an indication for anticoagulation, e.g., atrial fibrillation.
- *Durability:* Concerns regarding structural valve degeneration remains an important drawback of surgical and transcatheter bioprostheses (13). There is scarcity of evidence regarding the durability of bioprostheses in the tricuspid position however data from early experience are reassuring whilst we await long-term outcomes. In comparison, currently there is no data on TTVR durability. Hence, this will be a major issue when percutaneous treatment of the TV expands from compassionate cases to younger and lower risk patients with organic or functional tricuspid regurgitation.
- *Residual regurgitation:* The management of residual regurgitation after TTVR will be a major issue. The quantification of tricuspid valve regurgitation is still debatable and there is no clear threshold that is considered prognostic (14). The identification and quantification of residual insufficiency after TTVR is expected to be even more complex, and will require a comprehensive multi-parameter approach. Furthermore, since the TV annulus is saddle-shaped and has considerable systo-diastolic modification of its diameter, we can expect some type of incomplete apposition

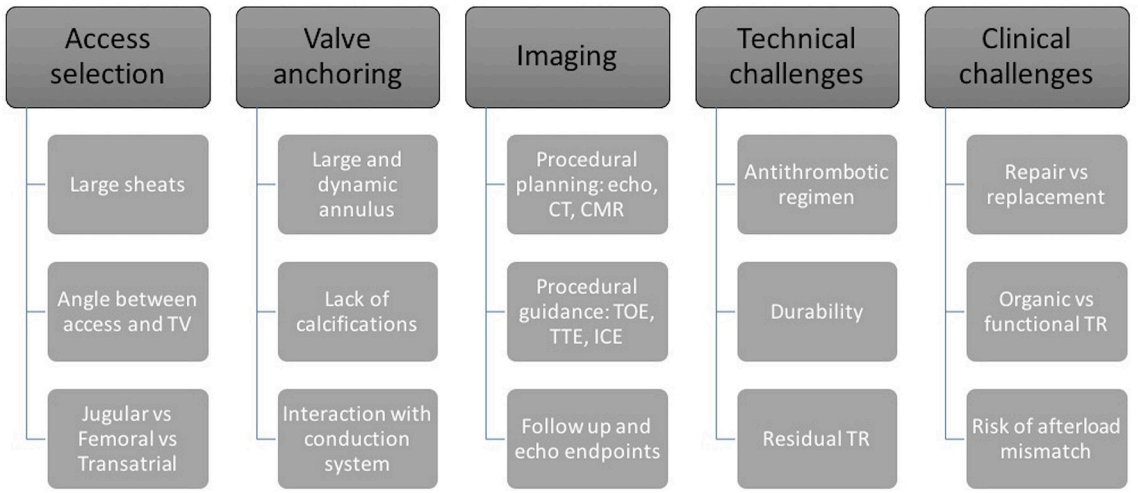

FIGURE 1 | Challenges of percutaneous tricuspid valve replacement. Systematic diagram outlining main challenges that will be encountered during percutaneous tricuspid valve replacement.

of the prosthetic valve, especially in the septal portion of the native annulus (11).

- *Acute increase in RV afterload:* Whilst tricuspid-valve replacement may eliminate the problem of residual regurgitation it can result in acute increase the right ventriclar afterload. In addition, RV dysfunction is common in patients with TR, either subtle or overt (15, 16) and is associated with adverse outcomes (17, 18). In the presence of RV dysfunction, it is assumed that abrupt discontinuation of the tricuspid regurgitation is associated with significant increase of the RV afterload. The RV is very sensitive to afterload changes (19). Thus, successful TV replacement may result in acute RV decompensation and adverse outcomes.

PATIENT SELECTION

A fundamental principle of all invasive procedures is patient selection. Surgical TV repair is the most common form of TV surgery and is predominantly performed concomitantly with another major surgical procedure (e.g., mitral valve surgery). Surgical TV repair is seldom performed for isolated TV disease (13% of surgical cases) (20). Furthermore, surgery for TR can be associated with a high risk of morbidity and mortality, with perioperative mortality reaching up to 10% in selected cases (1, 21). For these patients, new percutaneous transcatheter approaches may address this unmet clinical need. At present, percutaneous TV procedures may be considered in patients with severe TR who remain symptomatic despite optimal medical therapy. While various devices that mimic surgical repair have been evaluated in the last few years in clinical studies or for compassionate use, percutaneous valve replacement is still in an early stage (22). Similar to what is occurring with transcatheter mitral valve procedures, the parameters that may lead operators to prefer a valve replacement over a safe (although maybe less effective) repair procedure are still debatable. While there is still no clear evidence about this issue, we believe that reparative procedures may be less effective in the following subset of patients:

- TTVR may be preferred over repair techniques in those patients in where mechanism of TR is not functional. Fibrotic leaflets (as a result of carcinoid syndrome or of rheumatic disease) or large leaflet prolapse may be suitable of TTVR over repair.
- On the other hand, patients with extremely dilated annuli and/or with extreme leaflet tethering have low probability to be successfully treated with currently available repair devices unless annular and leaflet devices are combined. In these patients, tricuspid valve replacement may be the first option in order to offer the best result.
- Lastly, a fundamental aspect is pre-procedural evaluation of pulmonary hemodynamics and RV function: despite the lack of evidence, we can hypothesize that an acute reduction in TR in patients with severe RV dysfunction and severe pulmonary hypertension may result in acute afterload mismatch despite technical and procedural success (23). Ventricular afterload mismatch, defined as acute impairment of systolic function after mitral valve repair or replacement (both surgical or percutaneous), is well known in mitral valve surgery and is a major issue in patients with functional mitral regurgitation and reduced ejection fraction. While percutaneous approaches seem to reduce the risk and the severity of this phenomenon by avoiding factors like the effects of open-heart surgery, cardiopulmonary bypass, and cardioplegic arrest, its incidence is estimated to be about 25% in patients treated with MitraClip

(24). The RV is less able to tolerate acute changes in pressure, therefore the incidence and severity of afterload mismatch may be even higher, and this may hamper the acute efficacy of TTVR. Moreover, our ability to identify predictors of acute RV dysfunction remains poor (24). Indeed, the RV has a unique crescent shape, which adds complexity to the quantification of its size and function, thus making the effect of acute afterload increase less predictable. Furthermore, the treatment of left ventricular afterload mismatch is based on inotropic agents and arterial vasodilators; this class of drugs is known to be much less effective on the pulmonary circulation. All these aspects must be taken in account when planning TV procedures and may lead to patients with advanced RV dysfunction being excluded (or to prefer repair over replacement). In addition, these patients may require post-procedural support with inotropic agents or mechanical support in order to avoid organ failure and, eventually, death.

IMAGING FOR TRANSCATHETER TRICUSPID VALVE REPLACEMENT

Similar to mitral valve procedures, integration of interventional and imaging techniques is essential for TTVR. Cardiac imaging is essential at three crucial points: Pre-procedural planning (TR diagnosis, grading and etiology), interventional guidance, and follow-up after the procedure. The main imaging modalities are echocardiography (transthoracic, transesophageal, 3D echocardiography and intracardiac echo; **Figure 2**) (8), computed tomography (CT) imaging, and cardiac magnetic resonance (CMR). In this section the role of different types of imaging during the phases of tricuspid valve replacement will be discussed (**Figure 3**).

Tricuspid Regurgitation Evaluation and Pre-procedural Planning

TTVR requires accurate evaluation of the TV apparatus (with a particular focus on the TV annulus) and of the RV.

- Echocardiography plays a major role, allowing complete assessment of the TV as well as RV pathophysiology. Since the TV is the most anterior structure of the heart, transthoracic 2D and 3D are fundamental and usually offer good imaging due to low thoracic impedance. It allows good evaluation of TR severity and etiology, as well as RV function and pulmonary pressure. Transesophageal echo (TEE), especially with full 3D sets, may help defining the mechanism of TR and morphologically characterize the TV: detailed assessment of tricuspid leaflet morphology and function can be obtained, as well as TV annulus dimensions and function.
- Computed tomography imaging, with multiplanar 3-dimensional reconstruction, is essential for preprocedural TV structural evaluation. It allows precise measurement of the RV dimensions and TV annulus size, relation with right coronary artery and the distance between the TV annulus and RV apex. In addition, CT enables preprocedural fluoroscopic angulation calculation and assessment of the access site dimensions and course (e.g. subclavian and axillary veins) for TTVR (25). However, CT exposes patients to iodinated contrast media, that need to be considered during procedural planning in those patients with impaired renal function.
- Cardiac magnetic resonance imaging can be utilized as adjunctive imaging modality for TV assessment prior to TTVR. It can be used for anatomical and functional assessment due to its excellent spatial resolution. CMR imaging with dedicated RV planes provides detailed RV chamber evaluation that is comparable to 3-dimensional echocardiography; however unlike echocardiography it is not hampered by patient's body habitus or lung fields. In addition, for patients with atrial tachycardias or fibrillation, free-breathing CMR sequencing is effective in providing quantitative evaluation. CMR evaluation of TV leaflet morphology can be challenging because of the thin nature of the leaflets. Evaluation of the TV annulus can be performed using breath-held cine using multiple long-axis views. Moreover, offline multiplane reconstruction can be performed to get detailed anatomical evaluation of the TV annulus. Lastly, severity of TR can be calculated using indirect quantification (difference between the planimetered RV stroke volume and forward pulmonic flow volume) (25).

Procedural Guidance

Multimodality imaging is essential for percutaneous TV interventions. Identification of TV annulus, for instance, can be performed with echocardiography but a guidewire placed into right coronary artery may be a useful angiographic marker. Due to its anterior location, the TV is not always well visualized with TEE; however, this remains the first-choice procedural imaging modality. When in doubt, transthoracic echo may be useful. The role of intracardiac echocardiography is not clear yet, but it may overcome the limitations of TEE and may be useful in ensuring coaxial alignment of the valved-stent to the TV annulus before deployment (26).

Post-procedural Follow-Up

Once again, echocardiography has a key role in evaluation of procedural outcome. Echocardiography is able to evaluate not only the entity of regurgitation after TTVR that may be related to paravalvular or intravalvular jets, but also (and more importantly) the consequences of the insufficiency: RV reverse remodeling, regression of right atrial volume and inferior vena cava size may be used as surrogate endpoints of the success of the procedure (along with decrease in cardiac biomarkers like proBNP, creatinine, BUN, bilirubin and other liver enzymes). Postprocedural CT evaluation may be useful if there is uncertainty at follow-up echocardiography with regards to complications (e.g., device failure, detachment, leak, thrombosis) (26). The role of cardiac magnetic resonance is not clear yet, but we may hypothesize that it may be useful in those situations in which residual regurgitation grading is not clear.

Recommended Standard Imaging

Pre-procedural echocardiographic assessment including TEE and CT imaging evaluation are fundamental. Echocardiography enables hemodynamic and anatomical TV evaluation, and

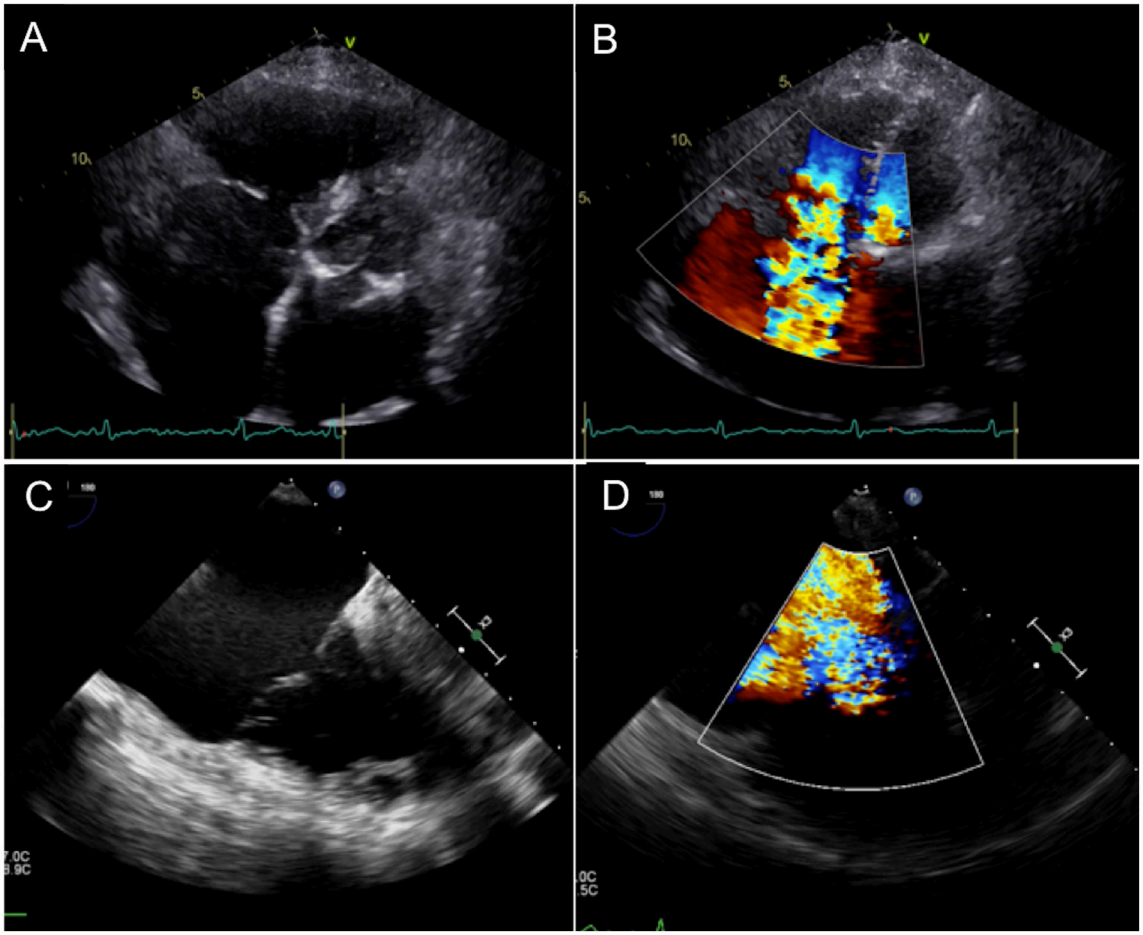

FIGURE 2 | Echocardiographic Evaluation of Severe Tricuspid Regurgitation and its etiology. **(A,B)** Extreme tethering and annular dilatation with loss of coaptation, resulting in severe valvular regurgitation. **(C,D)** Large posterior leaflet prolapse with severe eccentric regurgitant jet.

CT imaging permits precise device sizing and estimation of fluoroscopic angulations for the procedure. Intra-procedurally, fusion imaging (echocardiography and fluoroscopy) facilitates improved understanding of anatomical structures while showing enhanced visualization of catheter and device movements. In particular, it has a role in patients where technical difficulty is encountered and during initial learning curve implanting TTVR. Furthermore, in cases with poor transthoracic and transesophageal window we have found intra-cardiac echocardiography particularly helpful. It can be helpful for navigation inside right heart chambers, to visualize the device, to guide their fine positioning and orientation (coaxialization), and to discern the annulus from the leaflets.

TRANSCATHETER TRICUSPID VALVE REPLACEMENT DEVICES

While many companies are working on percutaneous tricuspid valve replacement devices, currently only a few have been successfully implanted in humans and there are a number of devices in development. The following section provides a brief overview of these devices.

NaviGate Prosthesis

NaviGate stent-valve (NaviGate Cardiac Structures, Inc, Lake Forest, CA) is a dedicated atrioventricular valve for the treatment of mitral and tricuspid regurgitation. It is a novel self-expanding valved-stent designed to treat functional tricuspid regurgitation and is available in sizes from 36 to 52 mm (**Figure 4**). It consists of a specifically configured Nitinol alloy stent into which is mounted a tri-leaflet valvular mechanism fabricated from equine pericardium. The configuration of the stent is specifically designed in a geometry that engages the TV annulus and TV leaflets from both inferior and superior aspects and maintains a minimal extension into both the atrium and ventricle to avoid flow dynamics alterations. Thus, the inferior aspect or ventricular diameter is designed to match the dilated TV annulus typical of secondary TR (27).

Initial pre-clinical feasibility studies demonstrated that the NaviGate is safe and feasible, and results in a secure

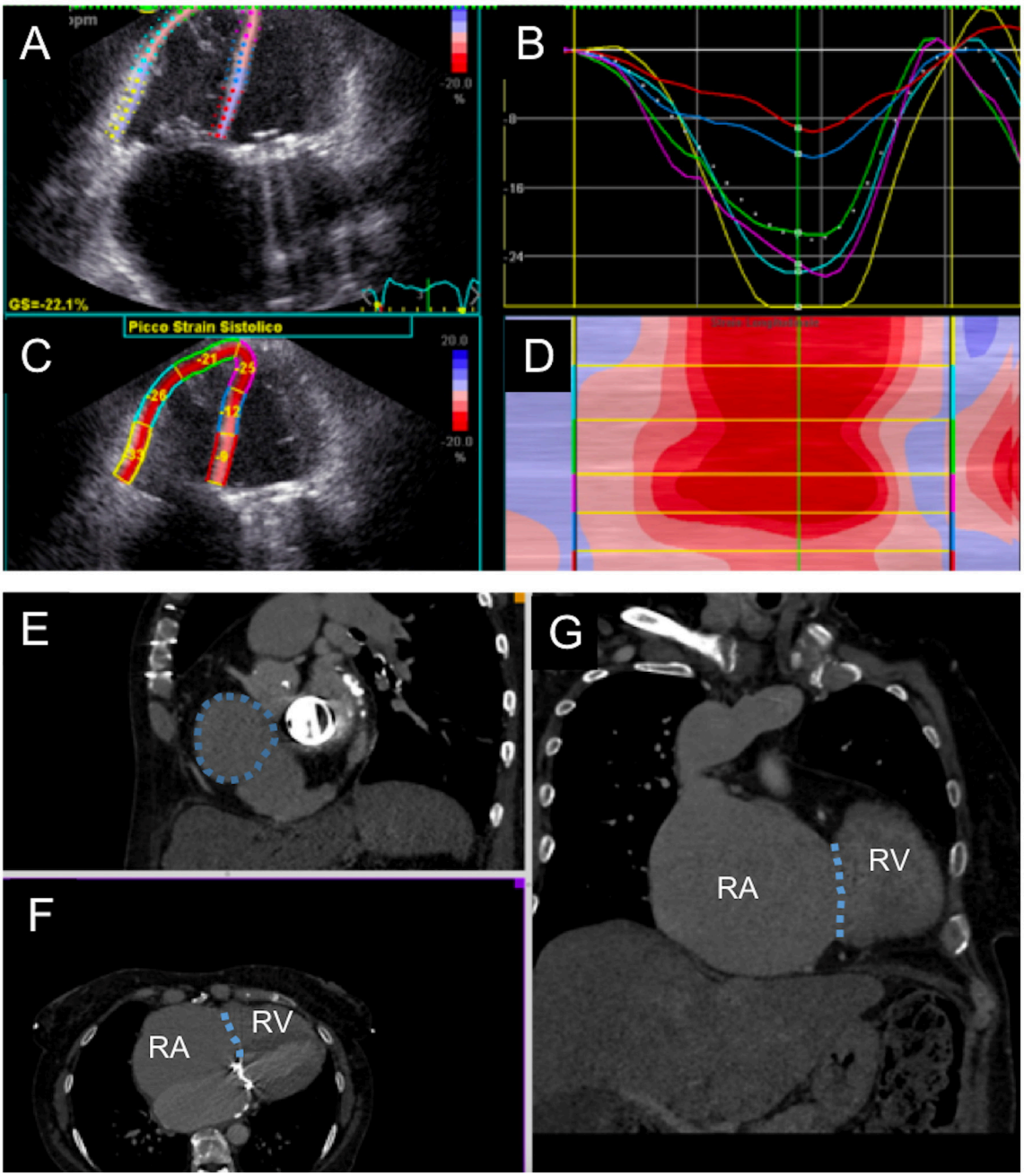

FIGURE 3 | Multimodality evaluation for percutaneous tricuspid valve replacement. **(A–D)** Echocardiographic evaluation of right ventricular function with semi-automated strain measurement. **(E–G)** Computed tomography cardiac chamber and tricuspid valve evaluation; the patient presented with severe right ventricular (RV) and right atrial (RA) dilatation; tricuspid annulus is highlighted with dotted line.

and stable engagement of the native annulus, with excellent hemodynamic and valve performance. There have been 27 cases of first-in-human successful implantation of the NaviGate prosthesis using the transjugular and transatrial approaches. The device size implanted were 36mm in 5%, 40mm in 5%, 44mm in 27%, 48mm in 27%, and 52mm in 36% of patients. Implantation of the NaviGate TTVR resulted in TR severity reduction from severe/torrential in all patients to ≤2+ in all patients, 78% having none/trivial postprocedurally.

An important consideration is that device oversizing by 5–10% to the TV annulus or prior TV ring size to achieve better

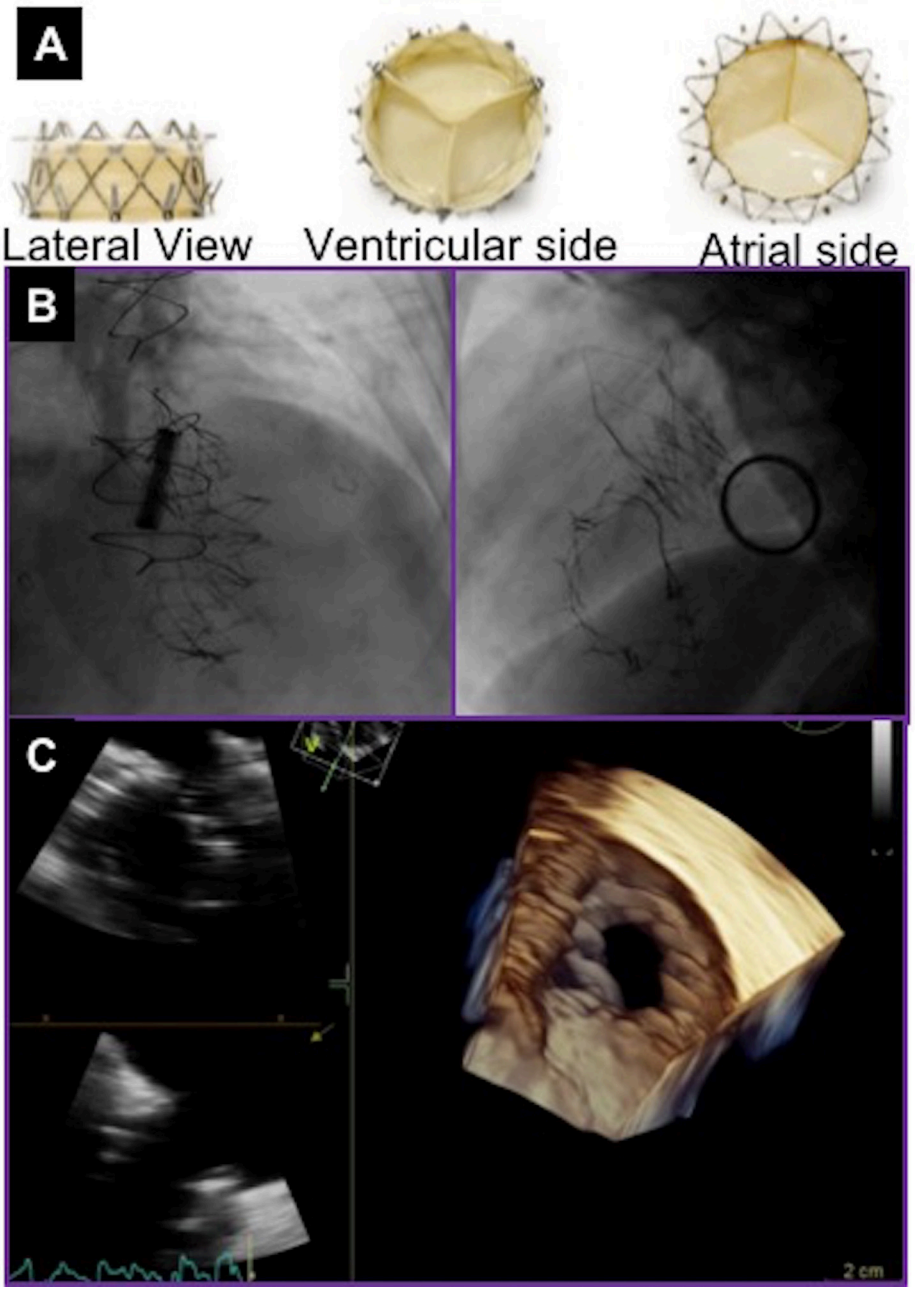

FIGURE 4 | NaviGate valve and final result after valve deployment. **(A)** NaviGate Valve Profile. **(B)** Fluoroscopic images of NaviGate deployed in tricuspid annulus with relative relations with mitral valve (previous mitral valve replacement) and aortic valve (previous transcatheter aortic valve implantation). **(C)** Echocardiographic images showing good expansion and stable position of the NaviGate Valve.

seal (9). To date, the NaviGate prosthesis has been implanted for symptomatic severe functional TR secondary to annular dilatation.

Trisol Prosthesis

The Trisol valve (TriSol Medical Ltd., Inc., Yokneam, Israel) is a novel percutaneous transcatheter valve representing a new concept in the treatment of severe TR (**Figure 5**). The TriSol valve is assembled as elastic nitinol frame and an inner valve apparatus. The nitinol frame is anchored to the annulus by multiple arms which are designed to secure the bioprosthesis into the native TV leaflets. An outside skirt seals the valve and prevents paravalvular leak. Anchoring with axial forces allows stability without affecting the conducting system. The valve apparatus is designed as a single bovine pericardial piece, attached to the nitinol frame in two opposite central

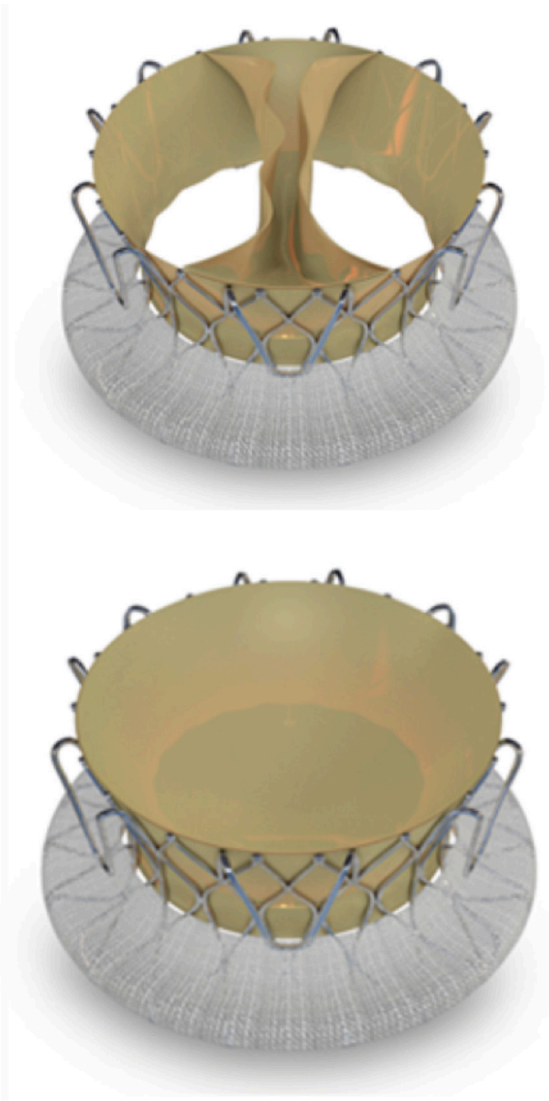

FIGURE 5 | Trisol valve. Elastic nitinol frame and an inner valve apparatus.

commissures, and functions as two separate leaflets. The leaflets move to the center of the lumen during diastole, enabling two large lumens for the diastolic filling of the RV. During systole, the two leaflets close and coapt to the full circumference of the tricuspid annulus. The leaflets close in a dome shape structure that increases the RV closing volume to about 20ml. This increased closing volume is expected to prevent the acute surge in afterload, and to better accommodate the concomitant RV dysfunction.

Tricuspid Prostheses in Development

The LUX-valve is a Chinese designed and manufactured self-expanding prosthesis made from bovine pericardial tissue mounted on a nitinol stent frame (**Figure 6**). It is implanted via the right atrium and the skirt is made from self-adaptive material to minimize paravalvular regurgitation. At present successful

FIGURE 6 | LUX-Valve. Self-expanding bovine pericardial tissue mounted on a nitinol stent frame.

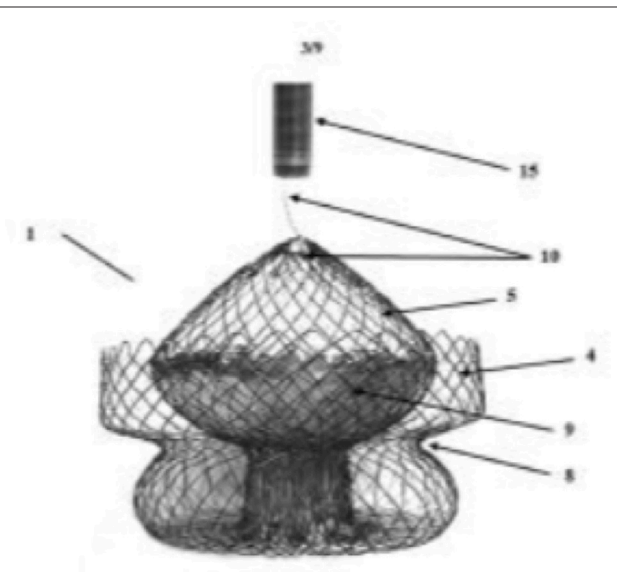

FIGURE 7 | Tri-cares valve. Schematic diagram of self-expanding prosthesis made from bovine pericardial tissue mounted on a nitinol stent frame.

implantation has only been demonstrated in animals. First-in-man study on the feasibility and safety of the LUX-valve is awaited. The Tri-cares (TRiCares GmbH, München, Germany) valve is a self-expanding prosthesis made from bovine pericardial tissue mounted on a nitinol stent frame (**Figure 7**). First-in-man study on the feasibility and safety of the Tri-cares valve is awaited.

CONCLUSION

Tricuspid regurgitation is a common condition in the general population and when of moderate-to-severe is associated with poor clinical outcomes. There is an unmet clinical need for intervention in these patients. Tricuspid valve replacement is an alternative therapeutic option for these patients. We are currently at an early stage of TTVR therapies for TR and expect this field to mature significantly in the next few years. Clinical studies with new TTVR devices will enable us to elucidate which patient population will benefit the most from TTVR.

AUTHOR CONTRIBUTIONS

OD, DR, GW, amd AL conception and design or analysis and interpretation of data, or both; OD, DR, AM, MA, SM, GW, AC, and AL: drafting of the manuscript or revising it critically for important intellectual content; OD and AL final approval of the submitted manuscript.

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PERSPECTIVE
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Treatment of Tricuspid Regurgitation With the FORMA Repair System

Gidon Y. Perlman[1]* *and Danny Dvir*[2]

[1] Hadassah Medical Center, Jerusalem, Israel, [2] Cardiology Department, University of Washington, Seattle, WA, United States

Background: Tricuspid regurgitation (TR) is common and undertreated as the risk of surgery is high in this patient population. Transcatheter devices offer treatment with a lower procedural risk. The FORMA Tricuspid Valve Therapy system (Edwards Lifesciences) will be reviewed here.

Device Description: The system combines a spacer placed in the regurgitant orifice and a rail, over which the spacer is delivered, that is anchored to the endocardial surface of the RV. The spacer provides a surface for leaflet coaptation.

Outcomes: Eighteen compassionate care patients and 29 patients included in the US EFS trial are reviewed. Patients were elderly (76 years) and high risk (Euroscore 2 was 9.0 and 8.1%, respectively). There were 2 procedural failures in both groups. Mortality at 30 days was 0% in the compassionate group and 7% in the EFS trial. TR was reduced in both groups; 2D/3D EROA 2.1 ± 1.8 to 1.1 ± 0.9 cm^2 in the EFS trial and vena contracta width 12.1 ± 3.3 to 7.1 ± 2.2 mm. Symptomatic improvement was seen in both groups; the proportion of patients in NYHA class III/IV decreased from 84 to 28% at 30 days in the EFS group, and from 94 to 21% at 1 year, in the compassionate group.

Conclusions: Reduction of TR with FORMA system is feasible and sustained. Despite residual TR post-procedure, the significant relative reduction in TR severity contributes to substantial clinical improvements in patients with a FORMA device in place.

Keywords: tricuspid regurgitation (TR), transcatheter, effective regurgitant orifice, FORMA, right ventricle (RV)

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Michael Chrissoheris,
Hygeia Hospital, Greece

***Correspondence:**
Gidon Y. Perlman
gidonpmd@gmail.com

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INTRODUCTION

Severe tricuspid regurgitation (TR) is a common and under-treated valvular pathology associated with increased morbidity and mortality (1–4). Recent data has shown that despite advances in surgical care over the years, surgery for isolated TR is rarely performed and operative mortality is still discouraging (5, 6).

Transcatheter therapies for TR have the potential advantage over surgery of reduced procedural risks, mainly due to reduced bleeding (from venous access sites) and reduced thoracic tissue damage, enabling easier recovery. Current transcatheter devices treat TR by improving leaflet coaptation or by modulating the annular geometry (7–12). The tricuspid valve apparatus is adjacent to both the right coronary artery (RCA) and the AV node; furthermore, the right atrium (RA) and right ventricle (RV) are thin walled and prone to injury from transcatheter devices. Performing percutaneous procedures for TR requires careful maneuvering around these structures to avoid injury, which has been reported after surgery (13) and with transcatheter devices (10, 14).

Patients with severe TR tend to have important co-morbidities. TR is associated with renal dysfunction that is often exacerbated by diuretics and hepatic congestion caused by TR can

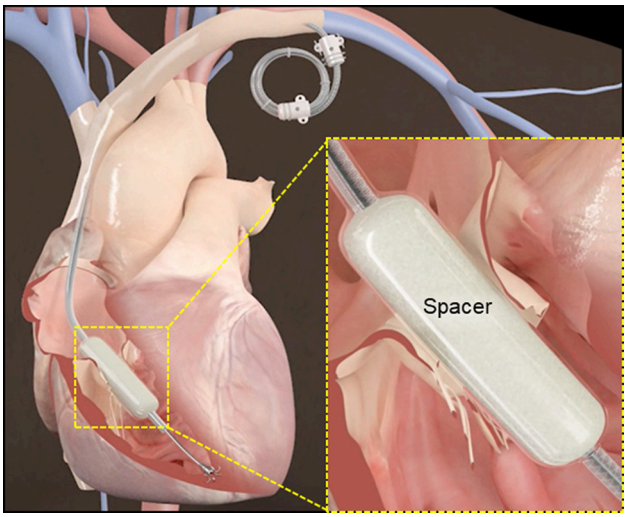

FIGURE 1 | Schematic representation of the FORMA system.

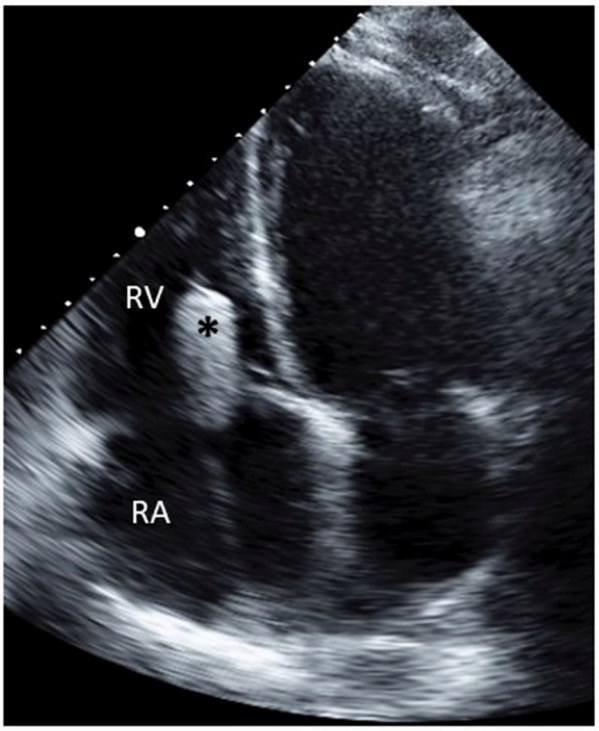

FIGURE 2 | Transthoracic echocardiography showing the FORMA spacer (*) positioned in the tricuspid valve.

lead to liver dysfunction. Atrial fibrillation is strongly associated with TR and patients often require anticoagulation for prevention of thromboembolic events. These conditions combine to put patients with severe TR at an increased risk of bleeding. Furthermore, chronic edema of the lower extremities which is the hallmark of right sided failure and contribute to significant impairment of ambulation. Taken together, the comorbid conditions of patients with severe TR can greatly impact the recovery and outcomes of patients after transcatheter TR repair.

The FORMA Tricuspid Valve Therapy System (Edwards Lifesciences, Irvine, CA) is a transcatheter device for treatment of patients with severe secondary TR. This review will present accumulating data on short and mid-term results of patients treated with this device.

Device Description

The Edwards FORMA™ system combines a spacer unit placed in the regurgitant orifice and a rail, over which the spacer is delivered, that is anchored to the endocardial surface of the RV (**Figure 1**). The spacer is a foam-filled polymer balloon that is round and tubular shaped, it is 42 mm long and has diameters of 12, 15, and 18 mm. When the spacer is positioned across the tricuspid annulus the native leaflets have a new surface for coaptation, thereby improving TR. Insertion of the spacer across the valve is done over a rail; the rail extends from the left subclavian vein to the RV apex. A nitinol anchor with 6 curved prongs is designed to grasp the RV myocardium without exiting into the pericardial space.

A 20F or 24F sheath is required for implantation of the FORMA system, through the sheath a dedicated delivery system is used to position the anchor and rail in the correct position. The delivery system can be flexed to navigate the anchor through valve and RV trabeculations. Close to the tip of the delivery system is a large balloon which is inflated prior to crossing the valve, to avoid entanglement in the valve chordae. The rail and spacer are fully retrievable using a specially designed retrieval system.

TABLE 1 | Baseline characteristics.

Characteristic	Compassionate care ($n = 18$)	EFS trial ($n = 29$)
Age, years	76 ± 9.7	75.9 ± 8.2
Female sex–No. (%)	13 (72)	19 (66)
Serum creatinine-mg/dl	1.5 ± 0.8	1.3 ± 0.4
NYHA functional class III/IV–No. (%)	17 (94)	25 (86)
EuroSCORE II	9 ± 5.7	8.1 ± 5.3
STS (for mitral valve replacement)	NA	9.1 ± 6.8
6 min walk test-meters*	256 ± 103	183 ± 96
Kansas City cardiomyopathy questionnaire*	63 ± 20	39 ± 22
Coexisting conditions-No. (%)		
Atrial fibrillation	16 (89)	24 (83)
Coronary artery disease	10 (56)	16 (55)
Prior CABG	7 (22)	9 (31)
Previous valvular intervention	9 (50)	14 (48)
Stroke/TIA	2 (11)	11 (38)
Chronic lung disease	5 (28)	7 (24)
Liver disease	1 (6)	9 (31)
Pacemaker/defibrillator	3 (17)	7 (24)

*Values are mean ± SD or n (%).*EFS data is for patients with paired data. CABG, coronary artery bypass grafting; TIA, transient ischemic attack.*

Implantation Process

The FORMA system is implanted under general anesthesia with transesophageal echocardiographic (TEE) monitoring, the details of the procedural steps have been previously reported (7, 14). Kodali recently reported the procedural outcomes of the US early feasibility study (EFS), procedural time in this group of patients was 110 min (15).

The procedure is divided to 4 main steps:

1. Venous access—Access to the left subclavian vein can be achieved by surgical cut-down or percutaneously with pre-closure with ProGlide (Abbott vascular) sutures. Patients with pre-existing pacemakers/defibrillators can be treated even if the generator is in the left delto-pectoral groove. Most patients with severe TR have congested veins that can accommodate the 20F or 24F sheath. Indwelling pacemaker leads can occasionally occlude the left venous system, can impede implantation of the FORMA system. The sheath is advanced to the left innominate vein/superior vena cava junction to support the delivery catheter.
2. Anchoring—The anchor target is on the lateral wall of the RV close to the interventricular septum. The anchor is positioned perpendicular to the annular plane to ensure optimal coaptation of the tricuspid valve leaflets. Manipulation of the delivery catheter in the RV is performed under fluoroscopic and TEE guidance to direct the catheter to the anchor site. TEE imaging of the anchor site is important to verify correct positioning and engagement of the anchor prongs in myocardial tissue.
3. Spacer positioning—After the rail is anchored to the RV the spacer slides down it to straddle the tricuspid annulus. The spacer self-centers in the regurgitant orifice, coaptation of the leaflets can be improved by minor adjustments of the spacer location and along the rail. When echocardiography and hemodynamic monitoring confirm adequate reduction of TR the position of the spacer is locked on the rail (**Figure 2**).
4. Rail fixation and access closure—The length of the rail is trimmed, and its proximal end is sutured to the subcutaneous tissue of the delto-pectoral groove to fixate the rail and the spacer. Venous closure is achieved either surgically or percutaneously.

TABLE 2 | Thirty day outcomes.

Outcome	Compassionate care ($n = 18$)	EFS trial ($n = 29$)
Death	0	2 (7)
Stroke	0	0
Myocardial infarction	0	0
Device related cardiac surgery	1 (6)	3 (10)
Bleeding		
Life threatening	1 (6)	2 (7)
Major	1 (6)	4 (14)
Vascular complications, major	0	1 (3)
Acute kidney injury ≥stage 2	0	3 (10)
Pulmonary embolism	0	0
New pacemaker	0	0
Device associated infection	0	1 (3)

Values are n (%).

Patient Population

Data on patient characteristics has been reported for 18 patients treated under compassionate care conditions (14) and 29 patients included in the US EFS trial (15). These patient populations can be characterized as high surgical risk. The Society of Thoracic surgeons (STS) score (calculated for mitral valve replacement) in the EFS trial was 9.1 ± 6.8% and the Euroscore 2 score was 8.1 ± 5.3%. The Euroscore 2 score of the compassionate care patients was 9 ± 5.7%. Patients in both cohorts were elderly (mean age 76) and predominantly women (66 and 72%). Multiple co-morbidities were common and prior left-sided surgery was present in approximately half (50 and 48.3%). Atrial fibrillation was present in 89% of the compassionate and 83% of the EFS trial patients. Pacemakers were present in 3/18 (17%) of the compassionate care and 7/29 (24%) of the EFS trial patients. Baseline characteristics are shown in **Table 1**.

Procedural Outcomes

Of 18 compassionate care patients reported there were 2 failed procedures, due to RV perforation in 1 patient and 1 early device dislocation in another. At 30 days and 1 year follow up there were no mortalities reported (14).

The adjudicated data on 29 patients in the EFS trial reported 2 procedural failures, both related to RV perforations. Two devices were explanted, because of detachment of the anchor in one patient (surgical explant) and because of endocarditis in the other

TABLE 3 | Echocardiographic results.

Characteristic	Compassionate care ($n = 18$) baseline	30 Days	*P*-value	EFS trial ($n = 25$)* baseline	30 days	*P*-value
TR vena contracta, cm	1.2 ± 0.3	0.7 ± 0.2	<0.001	1.6 ± 0.5	1.1 ± 0.4	<0.001
Effective regurgitation orifice area, cm^2	1.0 ± 0.6	0.4 ± 0.3	0.001	1.1 ± 0.6	0.6 ± 0.4	0.001
Tricuspid annular diameter, cm	4.6 ± 0.5	4.3 ± 0.5	0.09	4.4 ± 0.7	4.5 ± 0.9	0.58
RV diameter, base, cm	5.4 ± 0.5	5.0 ± 0.5	0.06	5.9 ± 0.9	5.5 ± 1.0	0.02
TAPSE, cm	1.5 ± 0.5	1.4 ± 0.3	0.44	1.4 ± 0.4	1.5 ± 0.4	0.59
Left ventricular ejection fraction, %	59 ± 9	61 ± 9	0.52	55.9 ± 13.8	58.6 ± 12.9	0.07

*Values are mean ± SD or n (%).*EFS data is for patients with paired data. TAPSE, tricuspid annular plane systolic excursion.*

(percutaneous explant on day 21). There were two procedure related deaths, as a result of RV perforation and as a consequence of the surgical explant (15). Thirty day procedural outcomes are shown in **Table 2.**

Echocardiographic Results

In the EFS trial 25 patients were available for echocardiographic follow up at 30 days. Core lab evaluation of TR showed reductions of TR, that were mostly in the range of torrential TR at baseline, by 49% when evaluated by 2D/3D quantitative effective regurgitation orifice area (EROA) 2.1 ± 1.8 to 1.1 ± 0.9 cm^2; and by 46% when using proximal isovelocity surface area (PISA) EROA 1.1 ± 0.6 to 0.6 ± 0.4 cm^2. Compassionate care patients treated with the FORMA system experienced similar reductions in TR severity (reduction of vena contracta width from 12.1 ± 3.3 to 7.1 ± 2.2 mm at 30 days), these measurements were site reported. Despite the short follow up, reductions in RV sizes were seen in both cohorts. In the EFS trial, Annular and RV base diameters were reduced (4.4 ± 0.7 to 4.5 ± 0.9 cm, P = 0.57 and 5.9 ± 0.9 to 5.5 ± 1.0 cm, P = 0.02, respectively) by 30 days. In the compassionate care cohort similar reductions were observed (annular diameters: 4.6 ± 0.5 to 4.3 ± 0.5 cm, P = 0.04 and RV diameters: 5.4 ± 0.5 to 5.0 ± 0.5 cm, P = 0.02). The echocardiographic results are presented in **Table 3**.

Functional Outcomes

Patients treated successfully with the FORMA experienced significant clinical improvements by 30 days in both the EFS trial and the compassionate cohort (**Figure 3**). In the compassionate cohort these improvements were sustained in the patients with 1 year follow up (n = 15).

In both cohorts the vast majority of patients (84 and 94%) were in New York heart association (NYHA) class III or IV at baseline, this was reduced by 30 days to 28% in the EFS trial patients and 6% in the compassionate cohort. Seventy-nine percent of the compassionate care patients remained in NYHA class I or II at 1 year. At 30 days, the average 6 min walk test improved by 39 meters in the EFS trial and 69 meters in the compassionate cohort. Similarly, the average Kansas City cardiomyopathy questionnaire heart failure score assessed at 30 days, improved by 29 points in the EFS trial and by 15 points in the compassionate cohort.

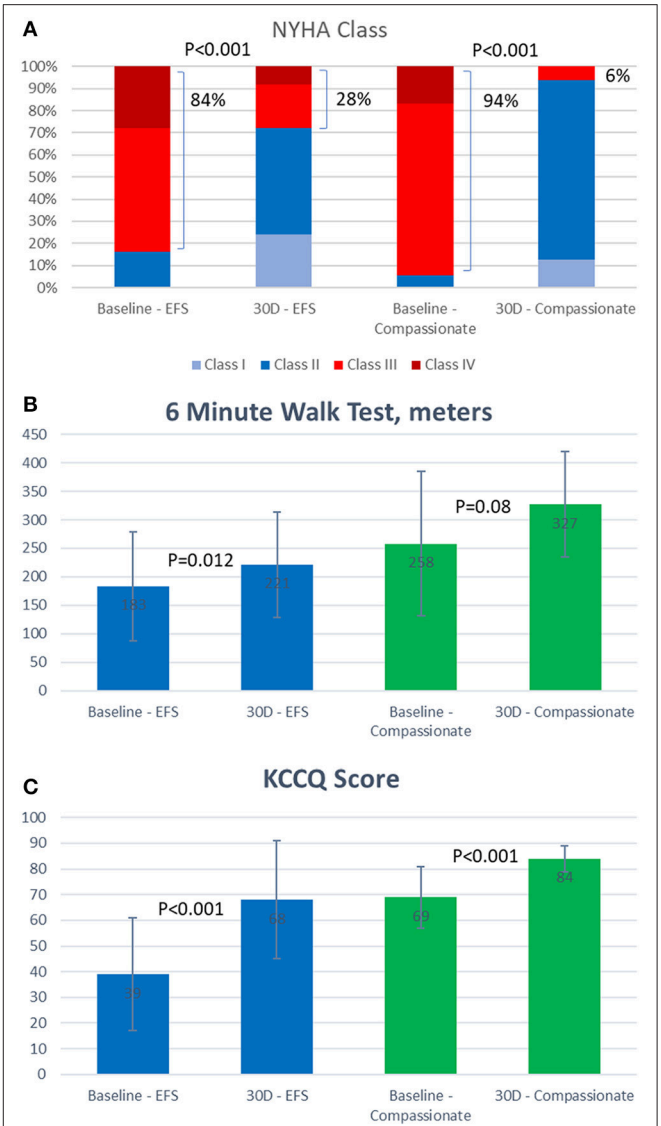

FIGURE 3 | Thirty day functional outcomes of patients treated with the FORMA device. **(A)** New York Heart Association (NYHA) class. **(B)** Six minute walk test results (meter). **(C)** Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

CONCLUSIONS

The tricuspid valve, long considered the "forgotten valve," is becoming a recognized target for transcatheter therapies aimed at treating symptomatic patients for whom there are no other viable options.

A striking similarity between the various devices is their positive clinical effect on the patients. Despite only modest reductions in the severity of TR reported in most studies, almost all reports of transcatheter devices show significant improvements in clinical outcomes such as NYHA class, 6 min walk test and heart failure scores. This is especially impressive given the fact that the patients treated generally extremely sick, with multiple co-morbidities.

The FORMA device acts as a spacer and thus seems independent of the size and shape of the annulus and the valve leaflets. The clinical experience with this device has been achieved in patients with extreme EROA's. Nickenig et al reported a PISA EROA of 0.9 ± 0.4 cm^2 in patients treated with the Mitraclip device (9) and Hahn et al. reported a PISA EROA of 0.51 ± 0.16 cm^2 in patients treated with the Trialign device (10). In the FORMA EFS trial, the mean PISA EROA was 1.1 ± 0.6 cm^2, with some patients having EROA's even larger than 2.0 cm^2.

Data on specific characteristics that may define a patient population more likely to respond to the FORMA device is still not available. Access to the left subclavian vein is required, patients with occluded veins may not be suitable for this device.

Additionally, patients with pacemaker leads that are adherent to the valve leaflet were excluded from the EFS trial, as this was considered to prevent coaptation of the leaflets with the spacer.

Anchoring the device to the RV is an important step of the procedure. The anchoring process requires adequate imaging and careful manipulation of the delivery system to avoid injuring the thin-walled RV. Refinements in implantation techniques and devices are needed to ensure the success of this step in a broader population of patients outside of controlled trials.

Further evaluation of the FORMA device is ongoing with expected inclusion of additional patients and refinements in anchoring techniques.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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The Conundrum of Tricuspid Regurgitation Grading

Yun Yun Go[1], *Raluca Dulgheru*[2,3] *and Patrizio Lancellotti*[2,3,4]*

[1] National Heart Centre Singapore, National Heart Research Institute Singapore, Singapore, Singapore, [2] Department of Cardiology, University Hospital Sart Tilman, Heart Valve Clinic, University of Liège, Liège, Belgium, [3] GIGA Cardiovascular Sciences, University Hospital Sart Tilman, Liège, Belgium, [4] Gruppo Villa Maria Care and Research, Anthea Hospital, Bari, Italy

Findings from early percutaneous tricuspid intervention trials have shown that the severity of tricuspid regurgitation (TR) far exceeded the current definition of severe TR. Also, the improvement in the amount of TR following tricuspid intervention is not accounted for by the current definition of TR as different degrees of severity at the severe end was grouped under the same umbrella term of "severe." There has been a recent call to expand the TR grading system, encompassing two more grades, namely "massive" and "torrential" TR, in the order of increasing severity. This seems appropriate as the patients enrolled in tricuspid intervention trials were found to have TR severity up to 2 grades above the current severe thresholds of effective regurgitant orifice area (EROA) 40 mm^2, regurgitant volume (R Vol) 45 ml and vena contracta (VC) width 7 mm. The proposed grade of "massive" is defined by EROA 60–79 mm^2, R Vol 60–74 ml and VC 14–20 mm, while "torrential" is defined by EROA $\geq$80 mm^2, R Vol $\geq$75 ml, and VC $\geq$21 mm. The grading of TR requires a comprehensive, multi-parametric approach. In particular, quantitative assessment of TR should be performed in patients who require serial monitoring and quantification of treatment effect.

Keywords: tricuspid regurgitation grading, massive tricuspid regurgitation, torrential tricuspid regurgitation, echocardiography, percutaneous intervention

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Edited by:
Fabien Praz,
Universitätsspital Bern, Switzerland

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Nicolas Brugger,
Universitätsspital Bern, Switzerland
Patric Biaggi,
Heart Clinic Zurich, Switzerland

***Correspondence:**
Patrizio Lancellotti
plancellotti@chu.ulg.ac.be

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INTRODUCTION

The tricuspid valve has often been labeled the forgotten valve, due to the lack of attention it received compared to its counterparts such as the mitral or aortic valve (1). Research interests and advancement in therapy, most notably percutaneous valve intervention for years seems to elude the tricuspid valve. In recent years, the tide appears to be turning. We witnessed a rise in interest and developmental breakthroughs in the treatment of functional or secondary tricuspid regurgitation (TR). The movement is both appropriate and timely as functional TR is a common but often-overlooked clinical problem. Severe TR is associated with increased morbidity and mortality (2, 3). Despite the poor outcomes, the number of patients with severe TR undergoing tricuspid valve surgery was dismal. Approximately 1.6 million patients in the United States live with moderate to severe TR and there are <8,000 tricuspid surgery performed annually (4, 5). The overwhelming majority of tricuspid valve surgery was performed during concomitant left-sided valve surgery (6). Among patients who underwent left-sided valve surgery, 37% eventually developed severe TR following rheumatic mitral valve replacement and 74% had moderate to severe TR 3 years after ischemic mitral repair surgery (7, 8). This not only speaks volume of the unmet

need for TR treatment, but also illustrates the treatment difficulty in patients with previous left-sided heart surgery who need downstream TR intervention, either in the form of redo surgery or percutaneous therapy. Last but not least, it highlights the importance of comprehensive and methodical echocardiographic assessment prior to or following any valve surgery.

ECHOCARDIOGRAPHIC ASSESSMENT OF TR

Echocardiography is the imaging modality of choice to assess TR severity and in turn, help to guide decision for treatment. The guideline-recommended echocardiographic assessment of TR is, however, not without its challenges. It involves a multi-parametric approach and calls for qualitative, semi-quantitative, and quantitative evaluation (9). Qualitative and semi-quantitative assessment are relatively straightforward and intuitive as they do not require multi-step calculations as quantitative approach does. As a result, many clinicians often adopt the qualitative or semi-quantitative approach, which give rise to two problems. First, it renders most comparisons, either serially over time or between patients difficult due to the lack of precision and standardization. Second, it is prone to under-estimation of the regurgitant severity.

Traditionally, TR is graded into mild, moderate, and severe, following the severity grading conventions that also apply to mitral, aortic, and pulmonary valves. Severe TR is defined quantitatively as an effective regurgitant orifice area (EROA) of $\geq$40 mm^2 and a regurgitant volume of $\geq$45 ml according to both the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) recommendations (9, 10). In particular, the EACVI recommendations made provision for massive TR. Massive TR is referred to as TR that is beyond severe and it is associated with a low TR jet velocity of $<$2 m/s as there is near equalization of right ventricular and right atrial pressures (9). However, in the EACVI recommendations, massive TR was defined qualitatively. There were no quantitative or semi-quantitative parameters that distinguish massive from severe TR and therein lies a 2-fold problem. For starter, the distinction between severe and massive is not always clear. Qualitative parameters such as the size of the TR jet on color Doppler can change substantially according to the Nyquist limits and loading conditions. Similarly, in the case of massive TR with very large regurgitant orifice area, a distinct color jet may not be apparent due to the presence of laminar, low velocity flow (10). Also, the use of descriptive terminology without proper standardization and quantification lacks the scientific rigor necessary for quality research. Terms such as very severe, free, massive, or torrential are descriptive and thus subjected to interpretation. Loose application or interchangeable usage of these terms are not uncommon both the published literature and clinical practice, making meaningful, quantitative comparisons impossible.

"Of note, the EACVI guidelines do not recommend EROA calculation using the quantitative PW Doppler method due to the lack of evidence that supports its use in TR quantification. The quantitative Doppler method however, has been used in mitral regurgitation studies and it systematically produces a larger EROA compared to PISA-derived EROA (11). Whether these findings can be extrapolated in patients with TR and if the cut-offs for severity grading are comparable warrant further studies."

REVISION OF THE CURRENT TR GRADING SYSTEM

In recent times, there has been a movement to revise the current TR grading, expanding the TR grading spectrum beyond severe to include "massive" and "torrential," in ascending severity (12). There are a few impetuses to expand the existing guideline-recommended TR grading. First, the rise of percutaneous tricuspid valve intervention trials and registry saw the enrolment of patients with TR far exceeded the severe limit defined by current guidelines (13). These patients had on average, TR with VC width, EROA or regurgitant volume one to two grades above the current definition of severe. Such magnitude calls to question the adequacy of the current definition at depicting the complete clinical picture. The lack of further distinction at the extreme end of the TR spectrum not only leads to non-discriminatory treatment of TR with different severity and prognosis, but also makes treatment effect difficult to detect. Natural history studies have shown that patients' prognosis worsened as the severity of TR increases, supporting the case for grading TR beyond severe to reflect the differential outcomes. This is particularly relevant among patients who received percutaneous TV interventions. After all, it is challenging to explain to patients that a therapy which improves their TR from severe to severe might still benefit them.

Some percutaneous TR intervention trials that included sick patients with torrential TR reported improvement in TR parameters equivalent to one full grade reduction or 20 mm^2 in terms of EROA (13, 14). There was also improvement in measurable clinical outcomes such as New York Heart Association (NYHA) class, quality of life and 6-min walk test. Although there was a lack of head-to-head comparison with patients treated with medical therapy alone in these trials, it is not unreasonable to associate these improvements with the reduction of EROA, reduction in tricuspid annulus size and increase in forward stroke volume, as a result of the intervention.

In the SCOUT (Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation) trial, the average quantitative EROA of the cohort was 85 mm^2 (13), which is more than 2 grades above the existing severe threshold of 40 mm^2, assuming a grade difference of 20 mm^2. Also, the average vena contracta (VC) of the SCOUT cohort was 13 mm, which is $\sim$2 grades above the existing severe threshold of 7 mm, assuming a grade difference of 3–4 mm. The transcatheter plication system produced a reduction of quantitative EROA of $>$20 mm^2, more than a full grade reduction of TR, which was both statistically significant and clinically meaningful. In the International Multicentre TriValve Registry, the average tricuspid EROA was 87 $\pm$ 56 mm^2 and the

TABLE 1 | Proposed tricuspid regurgitation grading.

	Mild	Moderate	Severe	Massive*	Torrential*
QUALITATIVE					
TV morphology	Normal/abnormal	Normal/abnormal	Abnormal/flail/large coaptation defect		
Color Doppler of TR jet	Small, central	Intermediate	Very large central jet or eccentric wall impinging jet		
CW signal of TR jet	Faint/parabolic	Dense/parabolic	Dense/triangular with early peaking	Peak TR velocity <2 m/s	—
SEMIQUANTITATIVE					
VC width (mm)§	<3	3–6.9	7–13.9	14–20	>21
PISA radius (mm)	≤5	6–9	>9	—	—
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal		
Tricuspid inflow	Normal	Normal	E wave dominant (≥1 cm/s)		
QUANTITATIVE					
EROA (mm^2) by PISA	<20	20–39	40–59	60–79	≥80
EROA (mm^2) by quantitative Doppler	—	—	75–94	95–114	≥115
EROA (mm^2) by 3D	–	–	75–94	95–114	≥115
R Vol (ml) by PISA	<30	30–44	45–59	60–74	≥75

TV, tricuspid valve; TR, tricuspid regurgitation; CW, continuous wave; VC, vena contracta; PISA, proximal isovelocity surface area; EROA, effective regurgitant orifice area; R Vol, regurgitant volume.
** further data required.*
§ preferably biplane.

TABLE 2 | Comparisons of current guideline vs. proposed changes to TR grading.

Proposed TR grading	Current guidelines
"Massive" for TR one grade above severe and "torrential" for the most severe form of TR possible	Made provision for massive TR qualitatively. No clear semi-quantitative or quantitative definition
Different thresholds for EROA obtained from PISA and quantitative Doppler methods	No distinction between EROA obtained from PISA and quantitative Doppler
EROAs and regurgitant volumes for massive and torrential TR were defined.	Only thresholds for severe (EROA ≥40 mm^2 and R Vol ≥45 ml) were defined.
Use of 3D vena contracta/effective regurgitant orifice area (the resultant value should be comparable to EROA obtained from quantitative Doppler)	No mention of 3D assessment
Use of biplane vena contracta	Did not emphasise the use of biplane vena contracta

average regurgitant volume was 63 ml, while the average VC was 11 mm (14), all at 1–2 grades above the current thresholds for severe TR, defined as EROA of 40 mm^2, regurgitant volume of 45 ml and VC of 7 mm.

The argument for the expansion of the current TR grading system stems primarily, although not solely, from the growing need to standardize and quantify transcatheter tricuspid treatment effect. With no specific criteria that capture the disease severity at the tail end of the TR spectrum, there is a risk of diluting measurable treatment effect. Currently, procedural success is defined as residual TR of ≤2+, successful implantation of device and patients being alive at the end of the procedure, similar to the definition used in mitral valve intervention. Only 62% of patients in the International Multicentre TriValve Registry achieved procedural success by definition and 51% of patients still had ≥3+ TR on discharge echocardiography. There was however, significant improvement in NYHA functional class and reduction in diuretic requirement at 30 days (14). The absence of a detailed grading system to quantify treatment effect may account for the discrepancy between the lack of significant TR grade reduction and the improvement of quality of life following successful percutaneous TV intervention.

It is inevitable that an improved TR grading system will be needed in view of the inadequacy of current definition. **Table 1** illustrates a proposed grading system, with emphasis on a systematic, multi-parametric approach. **Table 2** summarizes the improvements made in the new grading system compared to the current guidelines. It must be mentioned that the proposed TR grading system is based mainly on data gathered from percutaneous tricuspid intervention studies, which tend to be modest in study size and highly selective. The grading system therefore requires further refinement and support from large natural history, registry or outcome studies.

"In summary, there is no easy solution to the TR grading conundrum. Perhaps one that come close is to place heavier emphasis on quantitative assessment of TR. In the context of tricuspid valve intervention, this can be carried out by routinely report the EROA before and after the procedure in terms of

absolute or percentage change. An alternative, as proposed by Han et al. would be to expand the current grading system linearly by adding two more grades beyond the current definition of severe TR. More data, especially long-term outcome data is needed to resolve the conundrum."

CONCLUSION

TR has a wide disease spectrum, especially toward the severe end. A grading approach that emphasize on quantitative assessment account for the granularity of disease and give equal weightage to the full disease spectrum. It incorporates our new understanding of baseline TR severity and make allowance for measurable TR reduction in the era of percutaneous tricuspid intervention. It also introduces checks and balances, moving from subjective definition to a standardized lingo. In the foreseeable future, it is likely to have an influence on and in turn, be influenced by the design and evaluation of tricuspid interventional trials.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CASE REPORT
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Percutaneous Valve-in-Valve Treatment of a (Very Old and Fluoroscopy Invisible) Degenerated Tricuspid Prosthesis Through the Right Jugular Vein Approach

Cristina Aurigemma[1], *Francesco Burzotta*[1,2]*, *Michele Corrado*[1], *Christian Colizzi*[1] and *Carlo Trani*[1,2]

[1] Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCSS, Rome, Italy, [2] Università Cattolica del Sacro Cuore, Rome, Italy

Tricuspid valve dysfunction adversely affects prognosis and may cause severe symptoms. Among the different opportunity offered by transcatheter techniques, the valve in valve represents an emerging strategy to treat patients with degenerated surgical biological prosthesis. We describe a case report of a percutaneous valve in valve treatment of a very old and fluoroscopy invisible tricuspid degenerated bioprosthesis. In the reported case, pivotal issue for percutaneous valve in valve procedure success was the achievement of perfect alignment between transcatheter valve and degenerated bioprosthesis despite the horizontal right chamber axis and the poor valve visibility. Of note, the combination of jugular vein approach, transapical delivery system rotation, right ventricle guidewire placement, and right atrium angiography made the valve in valve procedure safely.

Keywords: tricuspid valve, degenerated prosthesis, percutaneous valve in valve, tricuspid regurgitation, tricuspid stenosis

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San Raffaele Hospital (IRCCS), Italy
Paolo Denti,
San Raffaele Hospital (IRCCS), Italy

***Correspondence:**
Francesco Burzotta
francesco.burzotta@unicatt.it

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A 71 years old woman was admitted to our hospital due to worsening congestive heart failure. Her long-lasting clinical history was characterized by rheumatic valve disease previously treated three times by cardiac surgery (1975: mitral valvuloplasty; 1982: mitral and tricuspid valve replacement with Liotta porcine bioprosthesis, 28 and 30 respectively; 1994: mitral valve replacement with mechanical valve and epicardial pacemaker implantation).

Echocardiographic examination showed tricuspid prosthesis degeneration with both severe stenosis and regurgitation (**Figure 1**). The right heart chambers were dilated and right ventricular dysfunction was present while normal left ventricular function and normal mitral mechanical valve function was documented. In heart-team discussion, cardiac surgery was ruled out due to prohibitive operative risk and compassionate treatment by attempt for percutaneous tricuspid valve in valve treatment was proposed as the most reliable option. After ethics committee approval and patient's written consent obtainment, the procedure was planned in our hybrid room. Of note, the tricuspid Liotta prosthesis was not visible at fluoroscopy. Trans-jugular access offers a good angle to approach the tricuspid valve, with a delivery system that requires less steering, but requires a vein large enough to accommodate the sheath without being damaged. The femoral vein is the safest access route due to its size, but the angle between the inferior vena cava and tricuspid valve is steep and may hamper the procedure. In our case the transcatheter tricuspid valve replacement was a

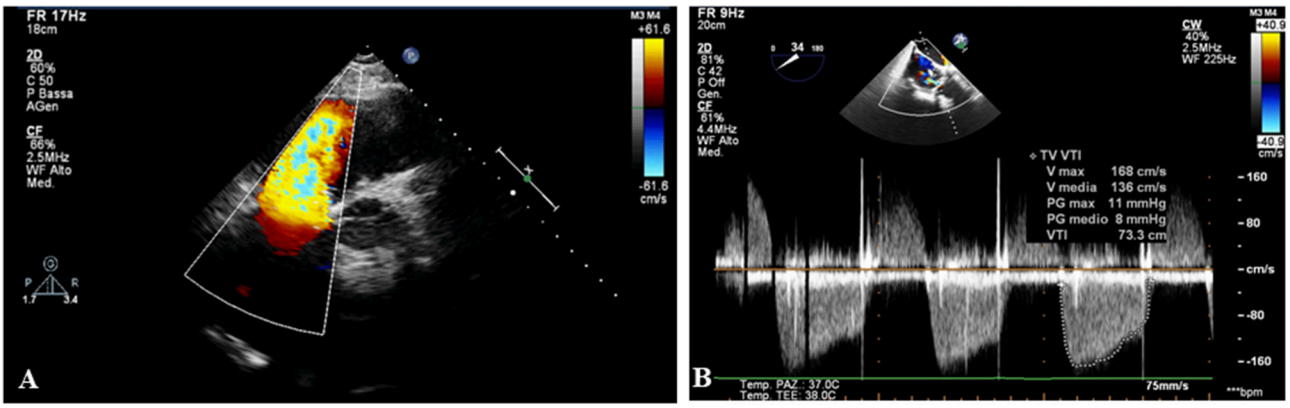

FIGURE 1 | The echocardiography shows a degeneration of tricuspid biological prosthesis with severe regurgitation **(A)** and stenosis **(B)**.

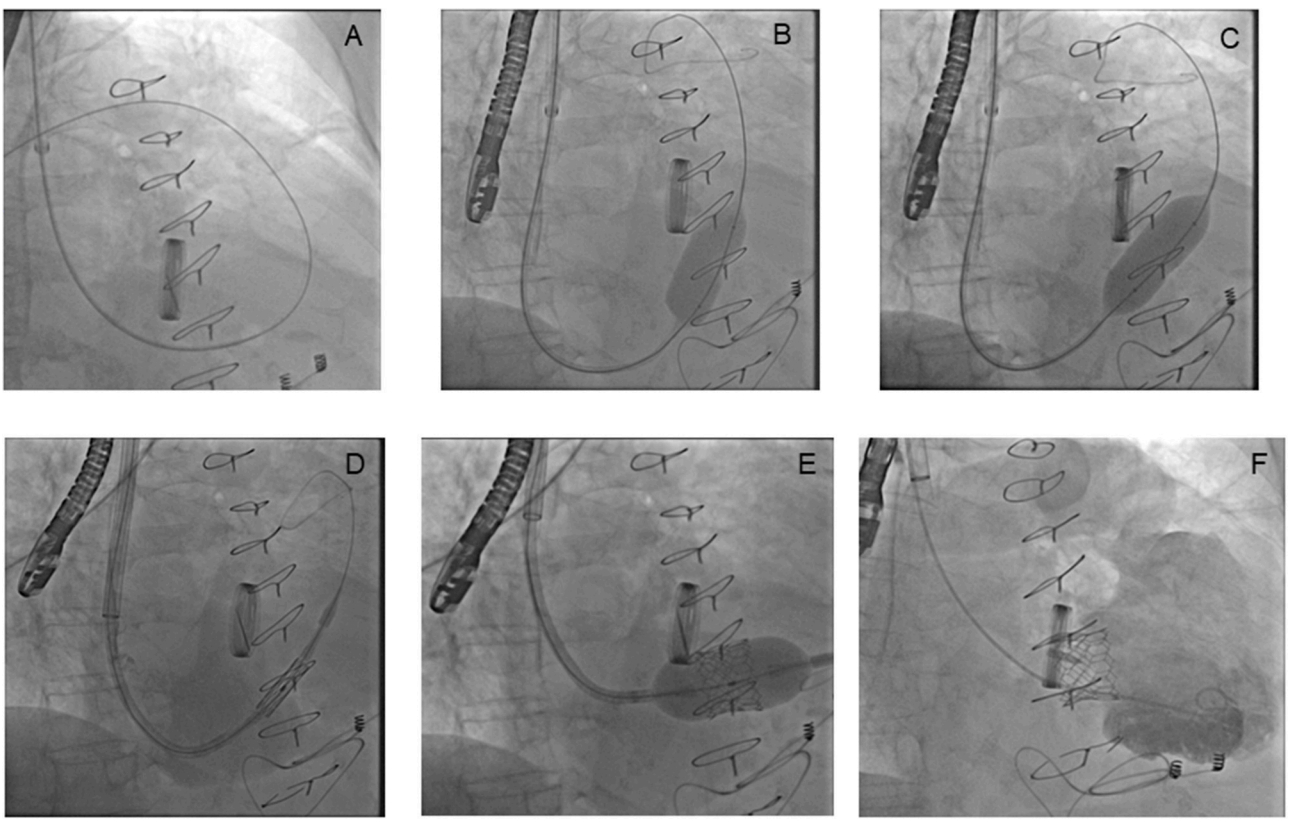

FIGURE 2 | The implantation of an aortic balloon expandable biological valve into a degenerated tricuspid biological prosthesis. A Swan Ganz catheter with an angiographic 0.035' wire crosses the tricuspid degenerated prosthesis **(A)**. A balloon valvuloplasty is performed, even if no mandatory in valve in valve procedure. The first balloon inflation shows a residual stenosis **(B)**, the second inflation shows a successful balloon expansion. The valvuloplasty is also performed to confirm the degenerated bioprosthesis size **(C)**. An aortic balloon expandable biological valve, a device normally used for aortic valve replacement, crosses the tricuspid degenerated prosthesis **(D)**. The guidewire is placed in right ventricle to achieve a perfect alignment between transcatheter valve and degenerated bioprosthesis despite the horizontal right chamber axis. The valve is deployed using a 3D transesophageal echocardiography (TEE) reconstruction and right atrial angiography to control the release **(E)**. The final right ventricular angiography shows no residual regurgitation after valve in valve implantation **(F)**.

valve in valve procedures and the dimension of the tricuspid bioprosthesis annulus was not large. Therefore, a right jugular vein was selected as the primary access (in order to facilitate coaxiality with the tricuspid prosthesis). A left jugular vein was selected as an additional access (in order to monitor right side pressures and administer drugs) and transesophageal

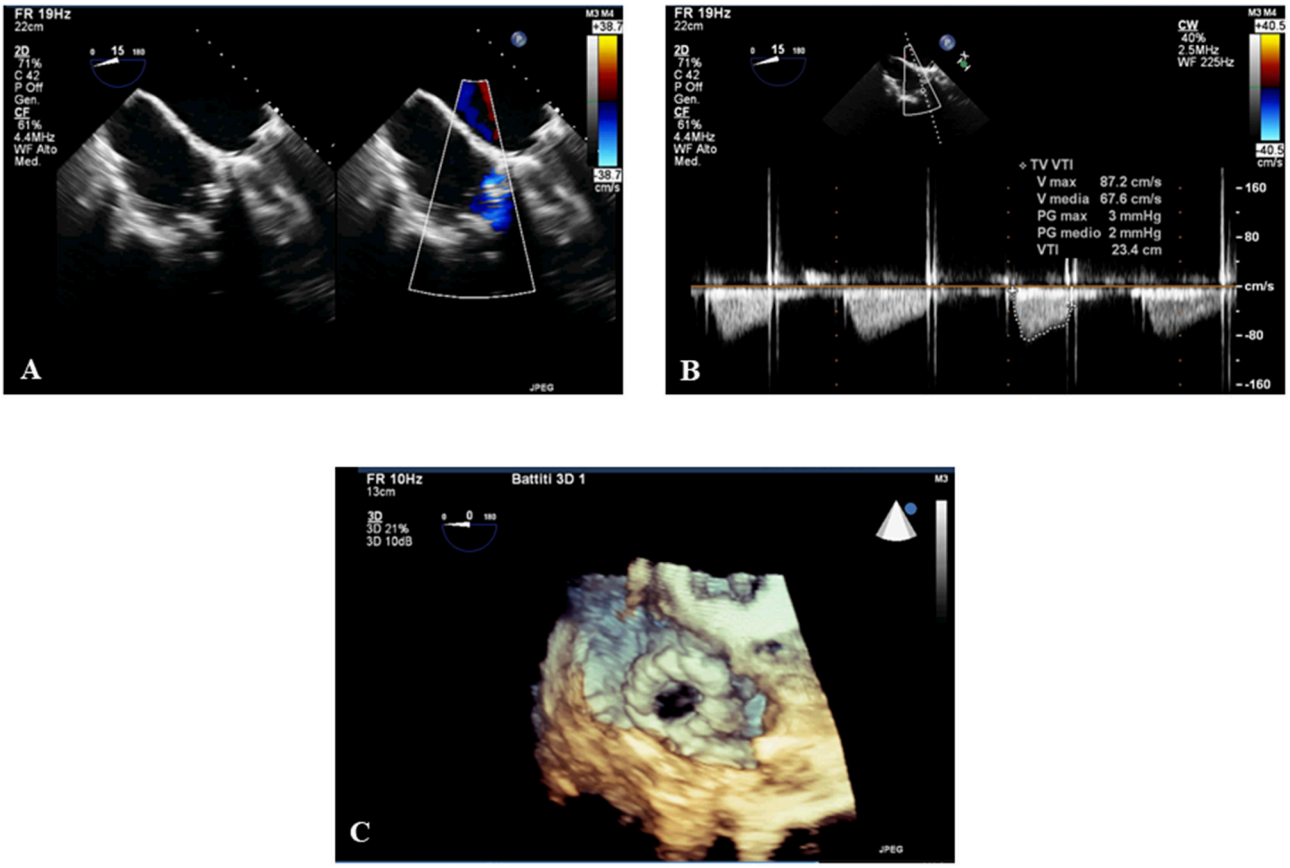

FIGURE 3 | The 3D transesophageal echocardiography (TEE) post procedure shows the normal function of the tricuspid valve. The 3DTEE post procedure shows the absence of regurgitation **(A)**, stenosis **(B)**, and the 3D reconstruction **(C)** of the tricuspid prosthesis after the valve in valve intervention.

echocardiography (TEE) monitoring was adopted to guide the procedure.

The tricuspid degenerated prosthesis was successful crossed by a Swan Ganz catheter with an angiographic 0.035' wire. Then, the angiographic wire was exchanged with a superstiff 0.035' wire (placed into the pulmonary artery system) which allowed to safely perform balloon valvuloplasty (using the 23 mm Edwards Balloon), (**Figure 2**). Even if pre-dilatation of the prosthesis is not mandatory in valve in valve procedures, we have decided to perform a balloon valvuloplasty to confirm the bioprosthesis valve size and to visualize a fluoroscopy invisible bioprosthesis. Then, on the bases of Liotta prosthesis internal measures, which was 30 mm in size, an Edwards Sapien 3 26 mm, a device normally used for aortic valve replacement, was selected to be implanted through the right internal jugular access using the 18F transapical delivery system. The transapical delivery system has been chosen because of its rotation system which could easily allow a better alignment with the degenerated valve despite the horizontal right chamber axis. Since neither fluoroscopy nor TEE allowed for reliable visualization of Liotta prosthesis, we decided to inject contrast media through the left internal jugular access obtaining a right atrial angiography which allowed precisely to control the valve in valve deployment (**Figure 2**; **Supplementary Video 1**). The TEE post procedure showed no regurgitation and no stenosis of the tricuspid valve (**Figure 3**). Post-intervention clinical course was uneventful and, on the seventh post-operative day, the patient was discharged.

Tricuspid valve dysfunction adversely affects prognosis and may cause severe symptoms. Yet, due to high surgical risk, it often remains undertreated (1). Recently, the rapid development of trans-catheter approaches, allowed to considering tricuspid valve patients with high surgical risk as potential candidates for percutaneous approaches (2). Among the different opportunity offered by transcatheter techniques, the valve in valve represents an emerging strategy to treat patients with degenerated surgical biological prosthesis in the left system. Recently a sub analysis of VIVID registry data has demonstrated that TTVR was also hemodynamically and clinically beneficial in patients of various ages and underlying disease states. Indeed in 306 patients who underwent TTVR adverse valve-related outcomes were relatively uncommon, and valve function remained excellent in the vast majority of patients followed beyond 3 years post-TTVR (3).

In the present case, we faced a patient with severe, symptomatic, prosthesis degeneration of a rare valve implanted in tricuspid position. The Liotta valve was in the past adopted

electively (by some surgeons) for the tricuspid replacement since its low profile allowed to minimize right ventricular cavity occupation (4). Yet, this porcine valve is uncommon and is not radiopaque thus making its percutaneous treatment particularly challenging. In the reported case, pivotal issue for procedure success was the achievement of perfect alignment between transcatheter valve and degenerated bioprosthesis despite the horizontal right chamber axis and the poor valve visibility. Of note, the combination of jugular vein approach, transapical delivery system rotation, right ventricle guidewire placement and right atrium angiography made the valve in valve procedure safely.

In conclusion, in the present case we have been able to successfully manage by valve-in-valve technique a degenerated tricuspid bioprostheses. The selection of appropriately sized aortic prosthesis and specific procedure adjustments may allow offer a percutaneous transcatheter treatment to patients with tricuspid prosthesis degeneration.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the Supplementary Files.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2019.00022/full#supplementary-material

Supplementary Video 1 | A right atrial angiography is performed to control the release because of neither fluoroscopy nor TEE allow for reliable visualization of Liotta prosthesis.

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REVIEW
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Imaging and Patient Selection for Transcatheter Tricuspid Valve Interventions

*Mirjam G. Winkel[1], Nicolas Brugger[1], Omar K. Khalique[2], Christoph Gräni[1], Adrian Huber[1], Thomas Pilgrim[1], Michael Billinger[1], Stephan Windecker[1], Rebecca T. Hahn[2] and Fabien Praz[1]**

[1] Department of Cardiology, Inselspital, University Hospital Bern, Bern, Switzerland, [2] Columbia University Medical Center/NY Presbyterian Hospital, New York, NY, United States

With the emergence of transcatheter solutions for the treatment of tricuspid regurgitation (TR) increased attention has been directed to the once neglected tricuspid valve (TV) complex. Recent studies have highlighted new aspects of valve anatomy and TR etiology. The assessment of valve morphology along with quantification of regurgitation severity and RV function pose several challenges to cardiac imagers guiding transcatheter valve procedures. This review article aims to give an overview over the role of modern imaging modalities during assessment and treatment of the TV.

Keywords: tricuspid regurgitation, valvular heart disease, tricuspid interventions, imaging of tricuspid valve, annuloplasty, edge-to-edge repair, caval stent, valve replacement

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Azeem Latib, Montefiore Medical Center, United States

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***Correspondence:**
Fabien Praz
fabien.praz@insel.ch

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INTRODUCTION

Since the recent emergence of percutaneous valve interventions as a possible alternative to surgery or medical treatment, tricuspid valve (TV) disease has attracted growing attention. Although tricuspid regurgitation (TR) of any severity is present in about 70% of the population (1), in the past this entity has been neglected in daily clinical practice. Severe TR affects around 4% of the population over 75 years of age, with higher prevalence in women, elderly patients, and in those who already underwent open-heart surgery for left-sided heart valve disease. This number is expected to rise in the future due to population aging (2–4).

Multiple observational studies have reported worse survival in patients with severe TR, irrespective of left and right ventricular function, pulmonary artery pressure, age, gender and co-morbidities (2, 5–10). In patients undergoing left-sided heart valve surgery or interventional treatment, the presence of relevant TR has been identified as a predictor of poor outcomes (11, 12). A recent propensity-matched cohort study showed that transcatheter TV interventions might be able to improve prognosis compared to medical treatment alone (13).

Imaging the TV and grading TR is challenging as transfer of existing knowledge and recommendations from the left side of the heart is not always possible. In contrast to the mitral valve, the TV operates in a low pressure environment with slower jet velocity. In addition, valve geometry, TR proximal flow convergence zone, and jet morphologies are more complex, making the usual tools and geometrical assumptions less accurate (14). The high variability of TR depending on small preload changes (e.g., during the respiratory cycle) (15), represents an additional difficulty (2, 16).

MORPHOLOGY AND ANATOMICAL RELATIONS

Autoptic studies have enhanced the anatomical understanding of the TV (17–19). Indeed, despite its name, the TV is truly tricuspid in only 57% of the investigated subjects (20). In the remaining 43%, it is quadricuspid with an additional leaflet, generally located between the septal and the posterior ones.

The healthy tricuspid annulus has a three-dimensional saddle-shaped elliptical geometry (15, 21–23). Its anterior and posterior portions are muscular, whereas the septal part is more fibrous, which explains predominant antero-posterior annular dilation as well as the spherical and planar shape of the annulus in patients with severe functional TR (11, 24). The tricuspid annulus is contiguous to several important anatomical structures (25). The postero-septal portion is close to the ostium of the coronary sinus, delimiting the triangle of Koch, where both the atrio-ventricular (AV) node and His-bundle are located. The antero-septal aspect of the annulus is situated next to the right ventricular outflow tract and the right coronary artery ostium. In its further course, the right coronary artery circumscribes the anterior and posterior portion of the annulus (11, 26) which exposes it to a risk of compression, kinking or occlusion during annuloplasty procedures, especially when located close to the hinge point of the TV leaflets. Although no data exist, a distance of <2 mm has been suggested as a possible cut-off and is found in 13–28% of the patients (27, 28).

ETIOLOGY AND MECHANISMS OF TR

TR etiology can be divided in primary (or organic) TR due to leaflet abnormalities, and secondary (or functional) TR due to annular and right atrial, or right ventricular dilation (25). Diseases leading to leaflet deformation can be either acquired, such as rheumatic or carcinoid heart disease, endocarditis, trauma, or congenital, like Ebstein's anomaly and endocardial cushion defect (29). Functional TR accounts for up to 94% of moderate to severe TR cases, with 49% occurring in the context of left-sided valvular disease, 23% concomitantly to relevant pulmonary hypertension (systolic pressure $\geq$50 mmHg), 13% in association with left ventricular dysfunction and 8% in isolation without any of the previously mentioned causes (2). Isolated TR was an independent predictor of all-cause mortality even after adjustment for various confounders (2). Increasing TR severity correlates with a higher cardiovascular mortality rate (2, 5, 9, 10).

TR leads to volume overload and further RV and RA dilation, resulting in annulus dilation, papillary muscle displacement and leaflet tethering, also influenced by elevated pulmonary artery pressure, further aggravating valve dysfunction (30, 31). TR not only has a mechanical effect on the right heart structures, but also increases stiffness of the RA, possibly due to chronic inflammatory processes and formation of interstitial fibrosis (32). Patients with associated right ventricular dysfunction, independently from RV dilation, have a particularly unfavorable clinical prognosis (33).

Chronic atrial fibrillation can be either the cause or the result of TR. Studies report a high overall prevalence of chronic atrial fibrillation in patients with moderate or severe TR (up to 68%) with a yearly incidence of 28% in the setting of associated left-sided valvular heart disease and 13% in isolated TR (2). Conversion to sinus rhythm may effectively reduce TR (34).

TR in the presence of cardiac implantable electronic devices-leads (CIED) is a topic of growing concern due to the rising number of implantations. New-onset significant TR after CIED placement has been observed in up to 38% of the patients, either resulting from direct valve injury or adverse interaction with the leaflets, most commonly affecting the septal leaflet (35), or the subvalvular apparatus (36, 37). Due to frequently associated left ventricular dysfunction and comorbidities acting as confounders, the causality of the higher mortality observed in patients with CIED-related TR is difficult to establish (38). The localization of the lead appears to influences the severity of TR. While a lead implanted in the interventricular septum has a higher risk of leaflet impingement, a more commissural or central position seems less problematic (37, 39). Interestingly, leadless pacemaker may also contribute to TV dysfunction because of either ventricular dyssynchrony induced by RV pacing or unintended interaction with the subvalvular apparatus (40, 41).

GRADING TRICUSPID REGURGITATION SEVERITY

Imaging the TV is associated with particular challenges summarized in **Table 1**. TR severity should be assessed in an integrative way using various echocardiographic parameters, as well as adjunctive imaging modalities such as multislice computed tomography (MSCT) and cardiac magnetic resonance imaging (CMR), when echocardiographic quality is poor or severity parameters are discordant (14).

Due to the anterior position of the RV close to the chest, transthoracic echocardiography usually provides satisfactory imaging quality for severity grading (42). Advanced anatomical

TABLE 1 | Challenges of imaging the tricuspid valve.

Challenges of TV Imaging
• Variable and fragile anatomy
• High (pre- and after-) load dependancy
• Low pressure environment / slower jet velocity
• Presence of CIED-leads
• Artifacts from left-sided bioprosthetic valves
• Limited evidence and experience
• Not or insufficiently validated cut-off values

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; AROA, anatomic regurgitant orifice area; CMR, cardiac magnetic resonance imaging; MSCT, multislice computed tomography; EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; RV, right ventricle; TV, tricuspid valve; TEE, transesophageal echocardiography; TR, tricuspid regurgitation; TTE, transthoracic echocardiography; VC, vena contracta; VCA, vena contracta area.

assessment typically requires a dedicated 3D transesophageal echocardiography (TEE) study owing to higher spatial resolution.

An integrative approach considering identical parameters using different imaging modalities is likely to improve the diagnostic accuracy.

Quantitative and semi-quantitative parameters considered useful for grading TR include the following:

Color Jet Area

Echocardiographic measurement of the color jet area using the 4-chamber, RV inflow or subcostal views is indicative of severe TR if the jet area exceeds 10 cm^2. It is physiologically influenced by direction, momentum and velocity of the jet and the systolic pressure difference between RV and RA (43), and technically by the color scale and wall filter settings, as well as the transducer frequency (14). Importantly, in very severe TR an early equalization of the pressure between the RV and the RA can occur, leading to a very low velocity with almost no visible jet (30).

Flow Reversal in the Hepatic Veins

Flow reversal into the hepatic veins is a specific parameter (if present: >85% probability of severe TR) (44), but with rather low sensitivity, as the venous flow patterns depend on various factors including RA dimensions and compliance, RV function, as well as atrial fibrillation or pacemaker stimulation (11, 30). A reflux of contrast medium into the inferior vena cava with enhancement of the mid to distal hepatic veins on MSCT is also considered highly specific for significant TR (45).

Tricuspid Inflow Velocity

Tricuspid inflow velocity can be used as a complementary method to grade TR. A peak tricuspid E-wave velocity >1.0 m/sec has been associated with right ventricular pathology (46) and severe TR (47). The tricuspid inflow velocity represents a simply obtained measurement, but has to be carefully interpreted in the context of age and heart rate.

Vena Contracta (VC)

VC is defined as the narrowest width of the color regurgitant jet and is usually measured directly below the proximal flow convergence zone. Severe TR is defined as a VC width $\geq$ 7 mm in the RV inflow view according to current guidelines, a value that has been associated with worse cardiovascular outcomes (1, 48–50). Due to triangular and elongated shape of the regurgitant orifice in TR, a single 2D measurement of the VC only insufficiently reflects the anatomical reality. Song et al. (51) have proposed the use of different VC width cutoff values for severe TR depending on the plane of the view: 8.4 mm in the septo-lateral and 12.6 mm in the antero-posterior view, respectively. Dahou et al. (52) have also suggested measurement in two orthogonal planes with an average VC cutoff of $\geq$ 9 mm. The VC widths measured in the septo-lateral projection were 3.9 $\pm$ 3.7 mm smaller than the one measured in the antero-posterior direction and discrepancies were found to worsen with increasing TR severity. To overcome these limitations, measurement of the 3D Doppler VC area using multiplanar reconstruction (**Figure 1**) may be considered (52, 53) Cut-offs for severe TR ranging from 0.37 to 0.75 cm^2 have been proposed (51–53).

Regurgitant Volume

The regurgitant volume can be derived from the stroke volumes (SV) assessed by quantitative Doppler and is calculated as the antegrade tricuspid diastolic SV minus the left ventricular or right ventricular outflow forward SV. In the presence of more than mild aortic regurgitation, the right ventricular forward SV should be preferred, and vice versa. In both cases, the SV is obtained from the diameter (D) and the velocity time integral (VTI) of either the right or left ventricular outflow tract as $(D/2)^2 \times \pi \times VTI$.

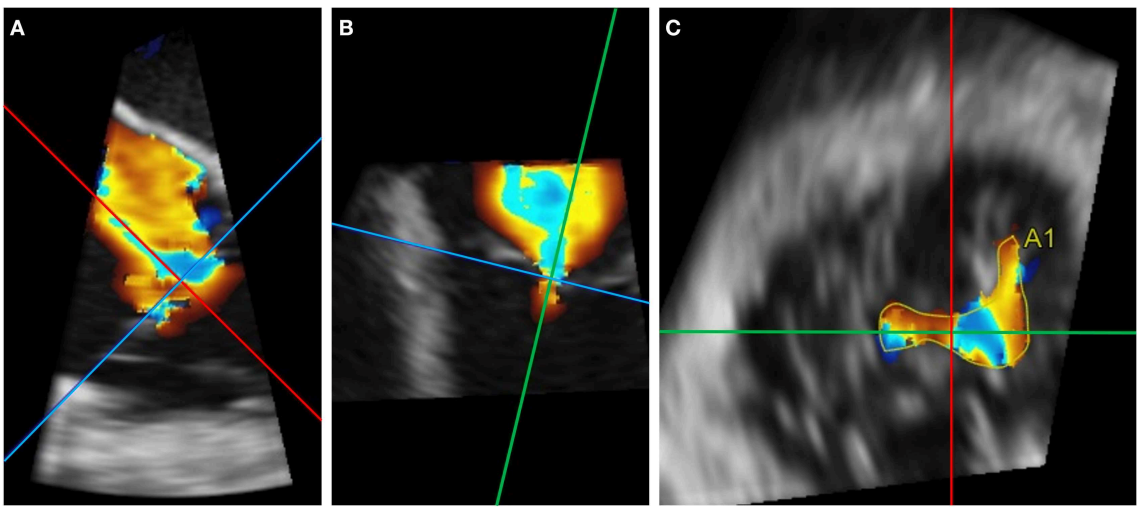

FIGURE 1 | Example of 3D Doppler VC area using multiplanar reconstruction. **(A,B)** Reformation planes are aligned at the height of the 2D vena contracta during systole in two different planes. **(C)** A1 measures 1.65 cm^2 in this case.

TABLE 2 | Example of a dedicated computed tomography protocol for the tricuspid valve.

Examination protocol for ECG-gated computed tomography of the TV
• 2 × 128 row stellar detector (e.g., Siemens SOMATOM Definition Flash)
• Inspiratory breath-hold, single-volume acquisition
• Retrospective ecg-triggered acquisition over the whole cardiac cycle (0–100% R-R interval)
• Isotrophic resolution 0.33 × 0.33 mm, crossplane 0.30 mm; gantry rotation time 280 ms; temporal resolution 750 ms
• Tube voltage 100–120 kV, tube current 240 reference mAs (care dose)
• Intravenous injection of non-ionic contrast agent (iopromide)
◦ 50 ml contrast medium at a rate of 4 ml/s, followed by
◦ 30 ml contrast medium at a rate of 3 ml/s, followed by
◦ 20 ml of saline at a rate of 4 ml/s
◦ total contrast volume = 80 ml
• Real-time bolus tracking with automated peak enhancement detection with region of interest ascending aorta, based on a threshold of 120 Hounsfield units
• Reconstruction of the 3D data set from the contrast-enhanced scan at 5% increments throughout the cardiac cycle with a slice thickness of 0.75 mm

The tricuspid diastolic SV by quantitative Doppler is calculated through multiplication of the tricuspid annular area (preferably measured on 3D multiplanar reconstruction) by the pulsed-wave Doppler VTI through the annulus (54, 55). The tricuspid diastolic SV may be overestimated in case of heterogeneous and complex annular flow patterns (54). Despite interobserver variability, the volume derived from quantitative Doppler assessment correlates well with other echocardiographic parameters (56) and has a prognostic value in patients with TR and reduced left ventricular function (8).

Using 4D MSCT the regurgitant volume and fraction are derived from the difference between RV and LV stroke volume obtained by ventricular volumetry. Higher saptial resolution may represent an advantage, but cutoffs to grade TR severity have not been established yet (14, 57). **Table 2** shows an example of a CT protocol dedicated to the tricuspid valve. The use of a mixture of saline/contrast is considered helpful to increase the contrast travel time and minimize streak artifacts (58).

Using CMR, the TR jet can be visualized based on its signal void with cine imaging. Quantitative TR severity is calculated indirectly. The forward flow volume is obtained from through-plane phase-contrast velocity mapping in the pulmonary artery. After substraction of the forward volume measured in the pulmonary artery from the total RV stroke volume assessed by RV volumetry (ciné steady-state free precession imaging), absolute TR regurgitant volume and fraction can be calculated (59). More recently, 4D-flow CMR has been used for 3D quantification of TR and can correct for through-plane motion as well as eccentricity, with high intra- and interobserver reproducibility and high consistency with 2D phase contrast velocity mapping and echocardiography (60, 61).

Effective Regurgitant Orifice Area (EROA)

Traditionally, an EROA by proximal isovelocity surface area (PISA) $\geq$ 40 mm² indicates severe TR. Calculation of the EROA according to the PISA method is based on the assumption of a circular orifice and thus disregards the complexity of the TV, resulting in underestimation of TR severity in one third of patients. Assessment of PISA by 3D-color echocardiography may overcome this limitation by providing a more realistic picture of the actual geometry of the flow convergence zone. However, it may underestimate the actual surface area of the PISA due to angle dependency of the color-Doppler. In addition, PISA only accounts for a single time point and therefore does not integrate the potentially dynamic nature of the flow (42). Alternatively, the EROA can be derived from the quantitative Doppler method, which has been shown to better approximate the planimetric 3D Doppler VC area (14). A possible implementation concept would be the assignment of different cut off values to PISA- and Doppler-derived EROA (52).

3D Integrated PISA

Instead of using a single PISA to calculate the regurgitant volume, the concept of integrated PISA accounts for temporal changes of the regurgitant flow during systole. With this method, a 3D PISA is reconstructed for each frame of the acquired loop. The flow of each PISA corresponds to its area multiplied by the chosen Nyquist velocity. As explained in **Figure 2**, the regurgitant volume is obtained by summation according to the duration of each frame. In patients with mitral regurgitation, it best estimates the regurgitant volume compared to CMR with high sensitivity (100%) and specificity (96%) for the detection of severe MR (62).

Anatomic Regurgitant Orifice Area (AROA)

As recently described for the mitral valve (63), measurements of the anatomic regurgitant orifice by CT are feasible and may be considered as an additional grading tool in patients with discrepant echocardiographic measurements.

In our experience, the values obtained using multiplanar reconstruction (**Figure 3**) are generally larger than the corresponding 3D Doppler VC area that rather reflects the effective regurgitant orifice after contraction of the flow stream. However, both parameters significantly correlate (**Figure 3C**), so that AROA may help to identify patients with severe TR.

Need for a New Grading Scheme

Since many patients present at a very advanced stage of the disease, current thresholds for severity grading may not sufficiently reflect the variability of the clinical presentation. For this reason, a new grading scheme including the two additional grades "massive" and "torrential" with corresponding cut-offs has recently been proposed (64, 65) and used in clinical studies (66, 67). Preliminary data show an incremental prognostic value of the new classification beyond "severe" (68, 69). In addition, the proposed scheme may allow better appraisal of the results following interventional procedures.

ASSESSMENT OF THE RIGHT VENTRICULAR FUNCTION

RV function has an important prognostic value in patients with TR (33) and, in the absence of elevated afterload, represents a marker of severity and duration of TR mediated volume overload.

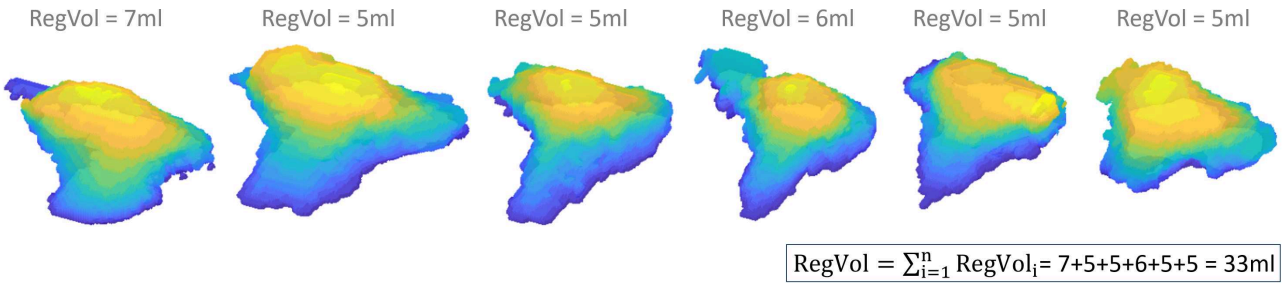

FIGURE 2 | Integrated PISA with three-dimensional reconstruction of 6 $PISA_i$ during systole using a Nyquist limit of 22.8 cm/s. This reconstruction highlights the complex shape of the TR PISA and its change in size and shape across systole. The following formula is used to calculate the 3D-$PISA_i$ flow: 3D-$PISA_i$ flow = 3D-$PISA_i^*$Nyquist-velocity. The $RegVol_i$ of each $PISA_i$ is derived using the duration of each frame (1/Volume rate, in this case 0.05 s): $RegVol_i$ = 3D-$PISA_i$ flow*0.05. The total RegVol is the summation of the $RegVol_i$ of each frame.

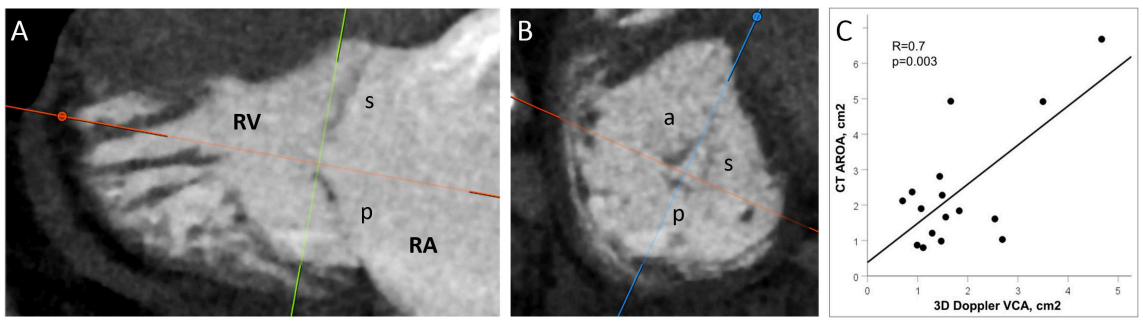

FIGURE 3 | Multiplanar reconstruction of the anatomic regurgitant orifice area (AROA) on MSCT images. **(A)** The reformation planes are adjusted at the leaflet tips during systole (20–40%). **(B)** The regurgitant orifice is delineated on the short axis. The AROA in this case is 0.7 cm^2. **(C)** Correlation between TEE color-Doppler 3D vena contracta area (VCA) and MSCT AROA obtained with multiplanar reconstruction.

CMR is considered the gold standard for evaluating the RV dimensions and function due to high spatial resolution and accurate volumetric 3D assessment (without the use of geometrical assumptions) (70).

RV ejection fraction is highly dependent on pre- and afterload, and for this reason, probably suboptimal for the evaluation of RV function in the presence of pulmonary hypertension and/or severe TR (57, 71). Tricuspid annular plane systolic excursion (TAPSE) and tissue-Doppler derived right ventricular excursion velocity (DTI) measured by transthoracic echocardiography are reliable compared to CMR (72). On the other hand, load dependency and variability according to measurement angle represent potential limitations (73). Moreover, the RV contractile pattern shifts after cardiac surgery further decreasing its reliability.

To overcome these specific drawbacks, new methods have been proposed. Using 2D spackle tracking, the longitudinal strain can be derived in all RV segments. This measure correlates well with the RV ejection fraction by CMR (74) and has been validated in patients with various cardiovascular conditions (75, 76) Recent studies have confirmed the high sensitivity of RV strain for the identification of RV dysfunction in the context of severe TR (77, 78). The right ventricular change in pressure over time (dP/dT), as assessed by echocardiography has been proposed as a novel parameter reflecting RV contractility and correlates well with CMR RV ejection fraction (77–79).

In contrast, 3D echocardiographic volumetric quantitation of the RV in different planes is limited by the need for clear delineation of the endocardial borders. Published data, which may overestimate the feasibility of this complex method, show a good correlation for systolic function, but a systematic underestimation of volumes in comparison to CMR (11, 73, 80).

Although less investigated, RV function, dimensions, and volumes may also be reliably obtained from a dedicated 4D electrocardiogram-gated MSCT (81) and normative values have been published (82).

PATIENT SELECTION AND PROCEDURAL PLANNING

Multimodality imaging is essential for patient selection as well as procedural planning. Moreover, it may help to anticipate and prevent complications and thereby improve outcomes. **Table 3** provides an overview of the specific roles of the different imaging modalities for pre-procedural planning and guiding.

TABLE 3 | Overview of the role of the different imaging modalities for preprocedural planning and intraprocedural guiding.

	Preprocedural	Intraprocedural
Echocardiography/ ICE	• TR mechanism and severity • Assessment of RV function • Estimation of RA and pulmonary pressures	• Visualization of catheters and leads • Identification of target points • Assessment of immediate result • Fusion imaging
Multislice computed tomography (MSCT)	• Measurement of annulus and RV dimensions • Asssessment of subvalvular apparatus • Localization of surrounding structures (CS, IVC, SVC, RCA) and implantation site • Implant simulation, 3D printing and access reconstruction	Calculation of optimal fluoroscopic viewing angles
Fluoroscopy	Angiography of RCA	• Navigation of access and in right atrium • Wiring and angiographic depiction of RCA • Valve deployment
Cardiac magnetic resonance	• TR severity • Assessment of RV function	–

Patient Selection

After thorough assessment of the underlying mechanism of TR, RV function and the exclusion of severe pulmonary hypertension, patients with persisting symptoms despite guideline-directed medical therapy should be evaluated for an intervention by the Heart Team. In patients with concomitant valvulopathy or coronary artery disease requiring surgical revascularization, open-heart surgery remains the first-line treatment. Patients at low surgical risk with isolated severe TR may also be referred for surgical valve repair or replacement, although evidence of an impact on survival is lacking (83, 84) In patients at increased surgical risk, transcatheter techniques may represent a valuable alternative with potential impact on outcomes in terms of heart failure hospitalization and mortality (13).

The surgical experience for valve repair has shown that a tenting area $\geq$ 1.8 cm^2, a tenting height $\geq$ 0.8 cm and a tenting volume $\geq$ 2 cm^3 are predictors of procedural failure for tricuspid repair (85–87). In a similar way, a coaptation depth $<$10 mm, a central or antero-septal jet location, as well as a coaptation gap of less than about 7 mm have been identified as independent predictors of procedural success for transcatheter interventions (88, 89). In contrast, procedural failure (reduction of TR of less than one grade) and elevated pulmonary pressures were identified as independent predictors of mortality (88). Although no study comparing different devices exist so far, specific system characteristics may better address a given pathology.

The selection of the appropriate transcatheter treatment solution should be based on the severity of annular dilation and jet location. Patients with predominant annular dilation and reasonable leaflet tethering are appropriate candidates for either an annuloplasty device [e.g., Cardioband (67) or TriCinch (90)] or leaflet approximation with either the MitraClip (66, 91, 92) or the Edwards PASCAL system (93). A dedicated system, the Abbott TriClip, is expected to be available soon. For treatment of a central jet, direct annuloplasty may be preferred, while patients with commissural TR are good candidates for leaflet approximation. On the other end of the spectrum, patients presenting late in the course of the disease with advanced RV remodeling, severe leaflet tethering or large coaptation gap should be evaluated for (bi-)caval valve implantation (94–96) or transcatheter TV replacement (79). However, in patients with advanced RV dysfunction, complete elimination of TR through replacement of the valve may precipitate RV failure and eventually lead to cardiogenic shock due to acute afterload mismatch, particularly in the context of preexisting elevated pulmonary vascular resistance and pulmonary hypertension (97). As pulmonary artery resistance may not be reliably reflected by the RV/RA-gradient or the mean invasive pulmonary artery pressure in the presence of TR, it should be calculated based on the values obtained during right heart catheterization. In cases of CIED—lead induced TR, decision should be made individually according to the above mentioned anatomic findings. Data from the TriValve registry showed comparable procedural success and clinical endpoints compared to patients without CIED lead (98).

Procedural Planning

A comprehensive echocardiographic assessment of the underlying TR mechanism, localization of the regurgitation jet(s) and if applicable, precise CIED-lead location and assessment of its relation to the leaflets (mobile vs. adherent) is crucial for procedural planning of any TV intervention. Especially the TEE short axis view, obtained from transgastric, or the surgical view, acquired by 3D imaging, delivers valuable anatomical information. When aiming for TV repair using leaflet approximation, the exact jet location as well the anticipated implantation strategy (triple orifice vs. bicuspidization), and the number of devices has to be determined. Coronary angiogram should also be part of pre-procedural work-up to confirm patency of the RCA.

Measurement of the TV annulus dimensions is another important step during planning of annuloplasty or valve replacement procedures. In contrast to the left side of the heart, annular dimensions correlate closely with TR severity due to the absence of a fibrous skeleton around the valve, and predominantly functional etiology of TR. A cutoff of $\geq$ 14–15 cm^2 for the annular area is indicative of severe TR (14, 99). The complex 3D elliptical shape of the TV annulus is best appraised by TEE or CT using 3D semi-automated imaging techniques that helps to minimize the impact of artifacts due to leads or left heart bioprostheses (11, 99).

According to a recent study, measurement of the tricuspid annulus by CMR is also feasible and reproducible (100).

PROCEDURAL GUIDING

Transcatheter tricuspid procedures are guided by 2D and real-time 3D TEE in combination with fluoroscopy, which enables

precise positioning of catheters and implants. Near-field views of the TV are obtained using deep transesophageal and transgastric positions of the TEE probe (101). A good acoustic transgastric short axis window is essential to ensure procedural feasibility. The different transcatheter techniques available have variable imaging requirements as detailed in **Table 4**. The combined skills of the interventional cardiologist and the imaging specialist are essential and equipollent for the success of the procedure. A consistent anatomical nomenclature has been proposed to facilitate intraprocedural communication (102).

Leaflet Approximation

Transcatheter leaflet approximation is mainly guided by 2D and 3D TEE (**Figure 4A**). For the orientation of the implant, a transgastric short axis view (30–50°) of the TV is typically obtained and allows for distinction of the commissures and orientation of the device (**Figure 4B**). Grasping is performed using an x-plane mid or distal esophageal view (50–75°) cutting either the antero-septal or postero-septal commissure (**Figures 4D,E**), while the implant orientation is monitored using fluoroscopy (**Figure 4C**). Bicuspidization or triple orifice technique have been proposed as possible strategies.

TABLE 4 | Role of imaging modalities for planning and guiding currently available transcatheter procedures.

	2D echo	3D echo	MSCT	Fluoroscopy
Leaflet approximation	+++	++	–	+ (+)
Annuloplasty	+++	+	+++	++
Valve replacement	+++	+++	+++	+
Caval valve implantation	+	–	+++	+++

Transcatheter Annuloplasty

Systematic MSCT analysis plays a crucial role for the planning and guiding of direct annuloplasty. This includes the calculation of optimal fluoroscopic viewing angles (**Figures 5A,B**), as well as the systematic measurement of the distance between the TV hinge point and the RCA (**Figure 5C**). Indeed, the RCA is at risk for injury during the procedure, especially if located in close proximity to the site of implantation. An "en face" view of the TV is typically obtained on an LAO fluoroscopic projection and allows for antero-posterior orientation alongside the RCA (**Figures 5B,D**) and corresponds to the TEE transgastric short axis view (103, 104). In this view, the ostium and proximal part of the RCA surrounds the anterior valve leaflet while the periphery is close to the posterior leaflet. As a further orientation landmark, but also to facilitate a tentative intervention, a coronary guidewire is placed into the RCA during

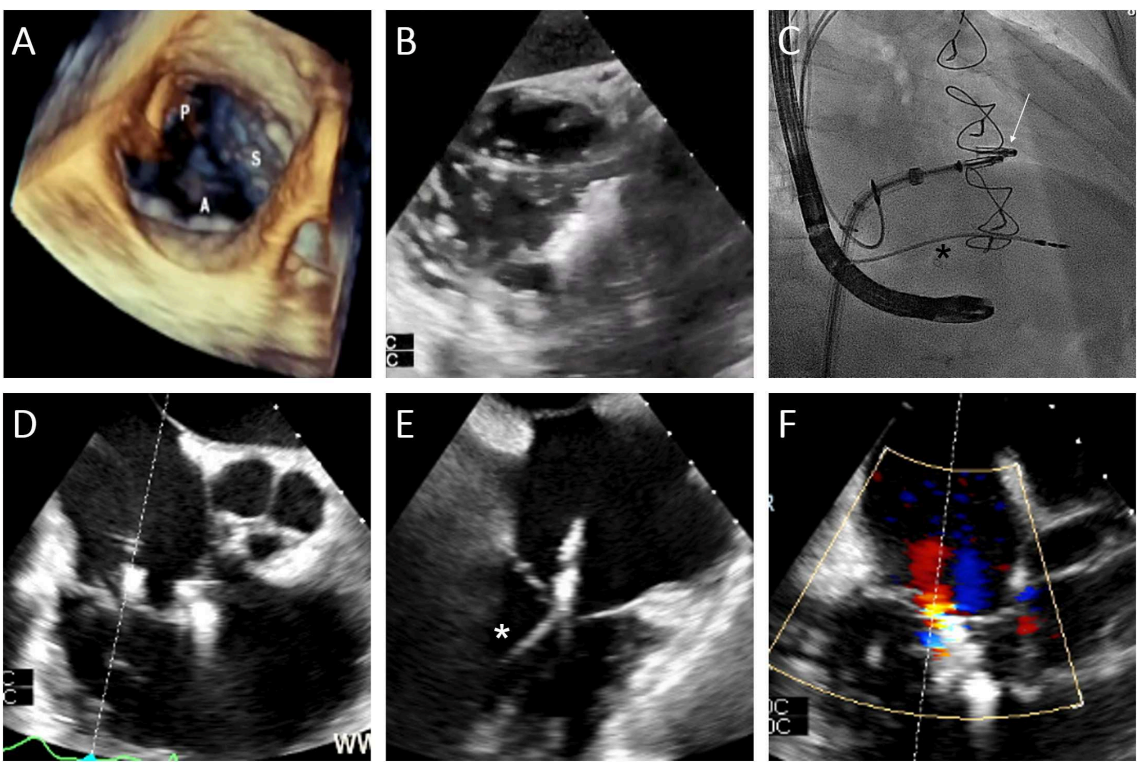

FIGURE 4 | Edge-to-edge repair case. **(A)** Assessment of the baseline valve anatomy using transesophageal 3D echocardiography (A=anterior leaflet; S=septal; p=posterior). **(B)** Orientation of the clip perpendicular to the antero-septal commissure using the transgastric view. **(C)** Insertion of the delivery system into the right atrium under fluoroscopic guidance (projection: RAO 20) after implantation of a MitraClip in the mitral valve (arrow). **(D,E)** Positioning of the clip in the postero-septal commissure using x-plane mid-esophageal view (closer to the aorta is a first clip in the antero-septal commissure, *pacemaker lead). **(F)** Final result after implantation of 2 clips.

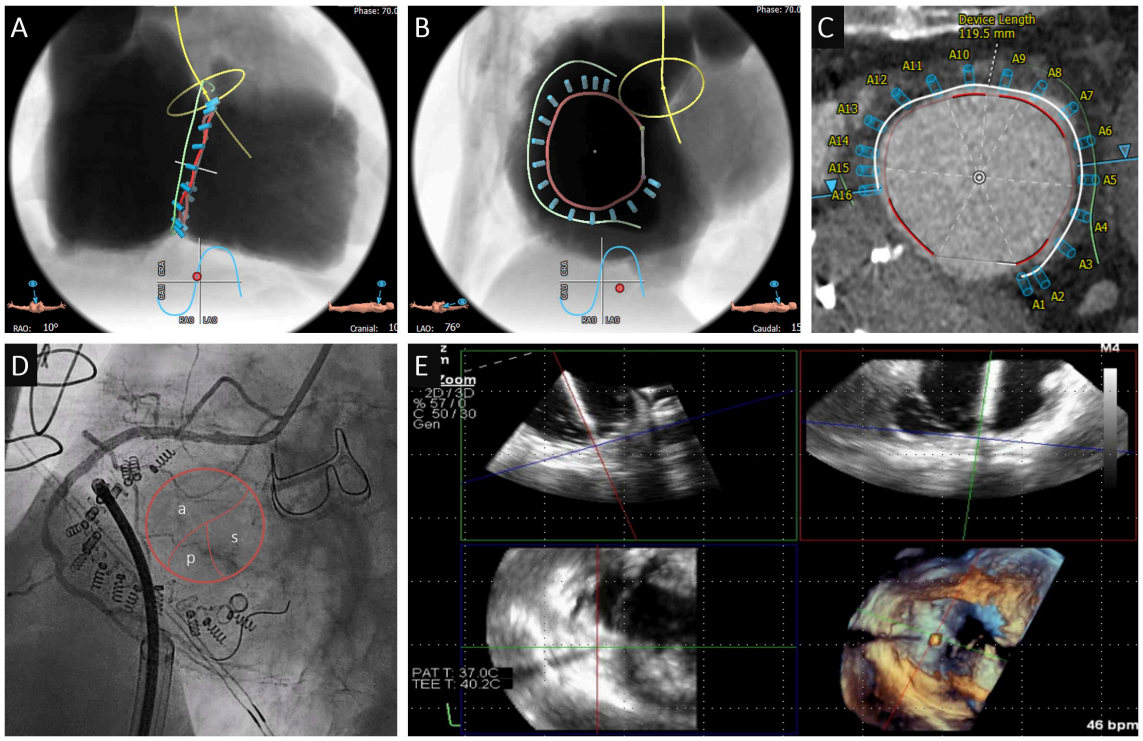

FIGURE 5 | Annuloplasty case. **(A–C)** Preprocedural MSCT planning of the Cardioband implantation (projection A: RAO 10—CRAN 10, B: LAO 76—CAU 15; green line: reconstruction of the RCA). **(A,B)** Anticipated localization of the screws in relationship with the RCA. **(C)** Measurements of the distance between annulus and RCA. **(D)** Angiography of the RCA after Cardioband cinching (projection: LAO 52—CAU 10) with "en face" view of the TV. The ostium and proximal part of the RCA are in close proximity to anterior leaflet while the periphery is close to the posterior leaflet. **(E)** MultiView echocardiography for intra-procedural guiding of screw implantation allowing catheter localization in three planes.

annuloplasty and valve replacement procedures. Visualization of the vessel helps to estimate the distance between the first screws and the aorta that is confirmed by TEE. A two-chamber view with the annulus and RCA in plane is generally obtained with a RAO caudal fluoroscopic projection (**Figure 5A**) and translates into a 110–130° low-esophageal RV inflow view in TEE (103). The relationship of each screw along the course of the RCA also inform about the position of the catheter in relation to the annulus (more atrial or ventricular). The use of biplane fluoroscopy and 3D echocardiography with multiplanar reconstruction (**Figure 5E**) enable simultaneous interrogation of several imaging planes.

Transcatheter Tricuspid Valve Replacement

Procedural planning of transcatheter tricuspid valve replacement requires detailed anatomic assessment of the tricuspid annulus including measurements of area and perimeter for appropriate valve sizing. Simulation may be used to anticipate access and final valve positioning. Centered position of the valve and deployment are controlled by transesophageal echocardiography (79), and optionally intracardiac echocardiography (105).

Caval Valve Implantation

For heterotopic caval valve placement, MSCT plays a central role to assess the dimensions of the right atrium, identify the ostium of the superior and inferior venae cavae, their angulation and dimensions, as well as the distance to the liver veins (**Figures 6A,B**). The procedure is then mainly guided by fluoroscopy (**Figure 6C**), while transthoracic echocardiography and possibly MSCT are used for clinical follow-up (106).

Adjunctive Imaging and Visualization Techniques

Intracardiac echocardiography (ICE) is increasingly used to guide transcatheter TV repair, currently as an adjunct to TEE (107–109). Placed in a low right atrial position it enables high resolution imaging of the TV and avoids artifacts from the left side of the heart. Current systems are limited by insufficient far-field imaging quality and the lack of 3D capabilities.

Fusion-imaging integrating echocardiography and/or MSCT, and fluoroscopy require further validation for tricuspid interventions. However, it has the potential to simplify the procedural steps through sophisticated visualization of anatomical structures and catheters/devices in relationship to each other (101, 106, 110).

MSCT provides the necessary information for 3D printing of anatomical models than can be used to simulate and train complex TV procedures.

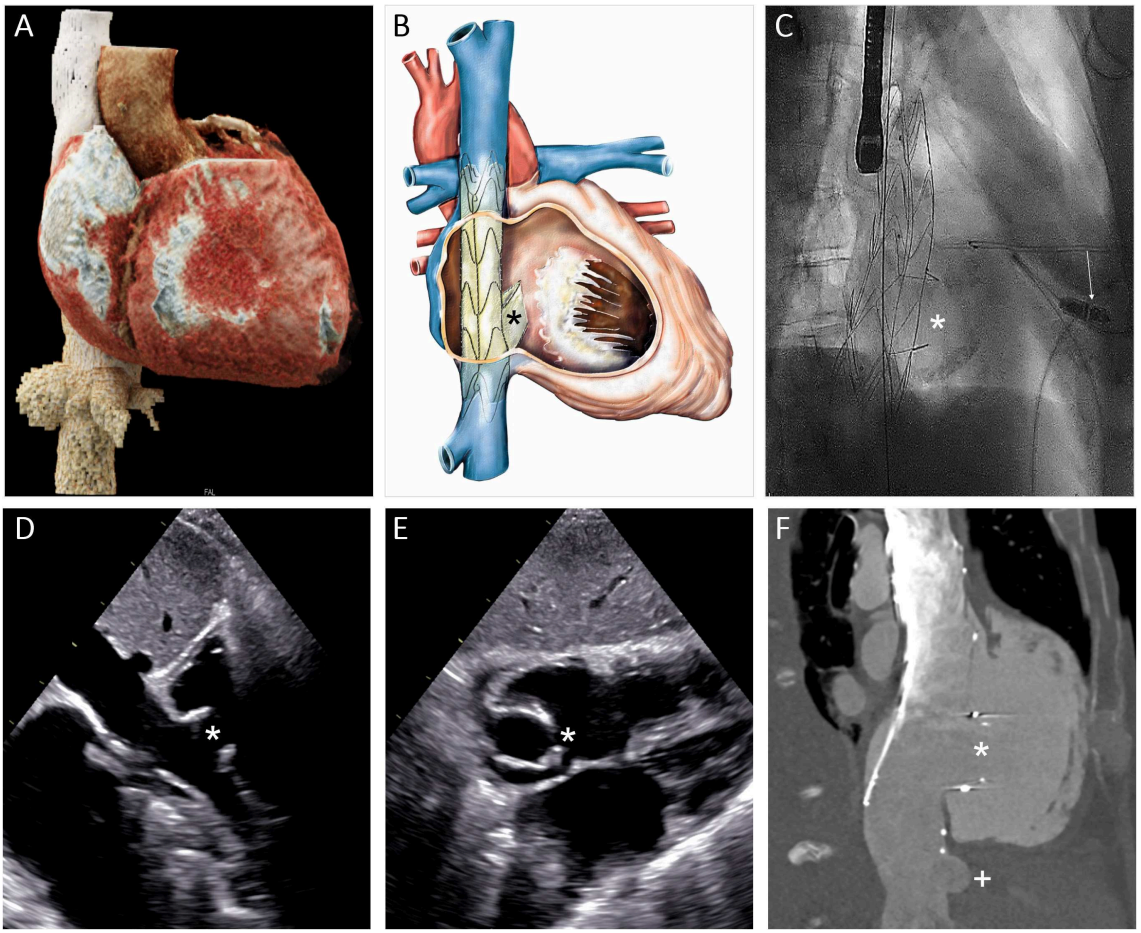

FIGURE 6 | Heterotropic transcatheter caval valve implantation. **(A)** 3D MSCT reconstruction of the vena cava inferior, the liver veins and the right heart cavities. **(B)** Schematic depiction of the NVT Tricento bicaval stenting device. **(C)** Fluoroscopic image of the implanted stent (projection: RAO 45). **(D,E)** Transthoracic echocardiographic imaging of the implanted device in his long and short axis from subxyphoidal at 30-day follow-up. **(F)** Depiction of the prosthesis and its relation to the right atrium and the hepatic vein in computed tomography. (Asterisk: valve element; arrow: leadless pacemaker; plus: hepatic vein).

ASSESSMENT OF RESULT

Assessment of interventional TR treatment efficacy using echocardiography can be challenging, especially after leaflet approximation procedures and/or when multiple TR jets are created. In addition, the implanted devices may produce acoustic shadows impairing correct evaluation of proximal flow convergence and vena contracta. Until now, only *in vitro* studies compared the echocardiographic evaluation of multiple regurgitant orifices with an independent method (111). From a theoretical point of view, only the PISA method (2D or 3D), the volumetric methods and the 3D VCA are appropriate for the quantitative evaluation of multiple regurgitant orifice by summation. Two-dimensional VC widths and jet areas cannot be summed. Changes of the hepatic vein flow patterns are also helpful. However, none of these parameters were tested against an independent method in this setting.

CONCLUSION

The tricuspid valve complex challenges imaging specialists and interventional cardiologists in many respects. Patients with TR constitute a heterogeneous and polymorbid population who frequently present late during the course of the disease. Imaging plays a crucial role for the understanding of the natural progression and underlying mechanisms of the disease, as well as for the guiding of transcatheter interventions. Further refinements of current imaging methods will help to better select the appropriate device for the right patient and simplify transcatheter procedures.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception of the work. It has been drafted by MW and FP

and has been critically revised by all authors for important intellectual content. All authors have given their approval for publication of the content and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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