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New clinical and pathophysiological insight in functional tricuspid regurgitation

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“ *Considerate la vostra semenza:*
fatti non foste a viver come bruti
ma per seguir virtute e canoscenza”

Dante Alighieri, Versi 118-120, Canto XXVI dell’Inferno, Divina Commedia

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OVERVIEW

The concomitant treatment of the tricuspid valve during mitral surgery has been matter of debate during the last decade. When left untreated a percentage of those patients developed during the follow up severe tricuspid regurgitation who is associated to reduced mortality and morbidity. The surgical treatment of this patients after development of severe tricuspid regurgitation and very often right ventricle dysfunction, implicates very high surgical risk.

The reduce the risk of late tricuspid regurgitation the guidelines for heart valve disease recommended tricuspid repair in case of less than severe tricuspid regurgitation, in case of annular enlargement, defined as diastolic annulus diameter of more than 40mm. This indication still comes from retrospective studies.

We performed a single centre prospective randomized study to investigate the role of additive tricuspid annuloplasty during mitral valve surgery. With subsequent analysis performed from this initial trial, we could identify new parameters to select patients who are at higher risk of tricuspid regurgitation progression after surgery. Using complex 3D echocardiographic methodologies, we could conclude that Is not much the annular dilatation who increase the risk of long-term outcomes, but more its function as surrogate of the right ventricular contractility.

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Introduction

Definition and epidemiology

Tricuspid valve regurgitation (TVR) is a type of heart valve disease in which the valve between the two right heart chambers (right ventricle [RV] and right atrium [RA]) does not close properly due to a mismatch between the leaflet surface at the moment of their closure and the total tricuspid valve (TV) area. This mismatch causes a regurgitant blood flow from the RV to the RA during systole.

The regurgitation process is defined as primary when the leaflets of the valve are affected by some type of pathological process resulting in modification of the leaflet anatomy, whereas secondary functional tricuspid regurgitation is present when the leaflets are normal, but the other structures, such as as right ventricle annuls or right atrium, are dilated.

In a general population analysis, tricuspid regurgitation (TR) was detectable in 82% of men and 85.7% of woman[1]. In a recent epidemiological analysis of the entire Swedish population using nationwide hospital-based registers, a total of 10,146,211 individuals was analysed, the incidence of TVR was the fourth most frequent valve pathology in the adults after aortic stenosis and both mitral and aortic regurgitation (MR and AR, respectively)[2] with a global incidence rate varying between 2.3 and 3 per 100,000 person-years. Diseases of the TV, aortic valve (AV), and mitral valve (MV) increase continuously with increasing age starting in the fourth or fifth decade of life with the peak incidence occurring in the seventh to eighth decade (Fig. 1). Heart failure (HF), pulmonary hypertension (PH), and atrial fibrillation (AF) were also common comorbidities in TR patients.

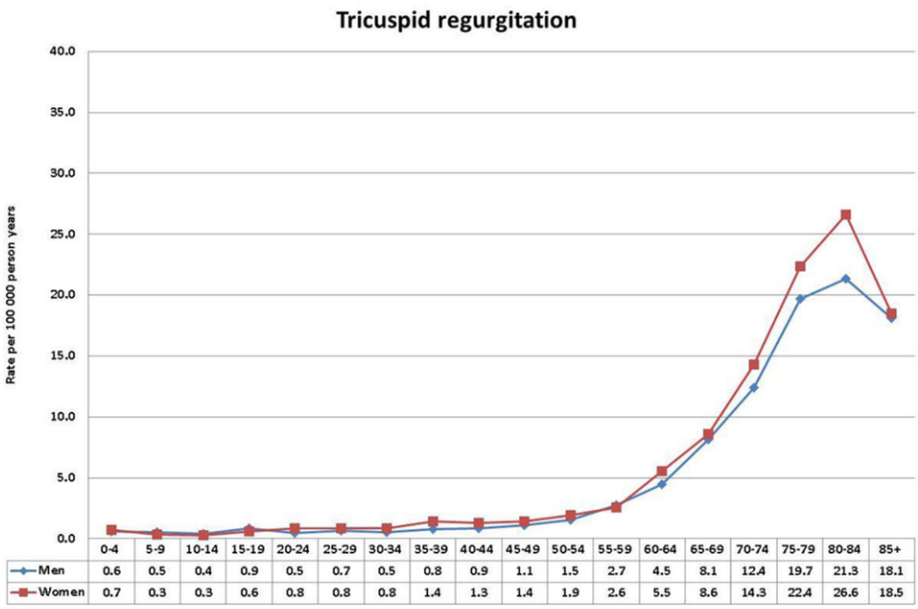

Figure 1. Incidence of tricuspid valve regurgitation from Andell et al. "Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study", Heart 2017;103:1696–1703

In an echocardiographic analysis of 33,305 patients consisting of both hospitalized and ambulatory patients at the Tel-Aviv Medical center[3], no or minimal degree of TR in 69.2% was detected. A mild degree of TR was present in 21.9%, moderate TR was present in 8% of the patients, and 0.8% had severe TR. When compared with patients who had no or minimal TR, those with at least mild TR were significantly older and had an increased prevalence of comorbidities, such as ischemic heart disease, AF , diabetes mellitus (DM), hypertension, lung disease, and renal dysfunction. More patients with at least mild TR had higher prevalences of additional valvulopaties; in cases of moderate or severe mitral regurgitation (MR), 18.9% of patients had this level of TR, while in cases of aortic stenosis (also moderate to severe), 31.7% had moderate to severe TR.

Some regional variations in terms of the prevalence of TR are apparent. Screening studies of elderly subjects have demonstrated a prevalence of moderate or severe TR of 2.7% in the United Kingdom (UK) and just 1.1% in China[4,5].

Studies describing the temporal trend in the epidemiology of TR have only recently become available. In an analysis of hospitalized subjects using the United States (US) National Inpatient Sample, the prevalence of TV disease from 2006 to 2015 showed an increase of 1.7% to 2% for all TR-related hospitalisations and from 3.9% to 5.7% in the hospitalisation rate for HF, particularly in those patients older than 85 years of age and female[6].

An aetiological distribution pattern of TR in a recent analysis of community residents in Olmsted County identified 1095 patients with greater or equal to moderate TR (out of 21.021 Olmsted County residents that had echocardiographic exams from 1990 to 2000). The most common TR-related aetiology was functional TR secondary to left heart valve disease (n = 542; 49.5%) followed by functional TR associated with PH unrelated to any heart disease (n = 252; 23%), functional TR related to left ventricle (LV) systolic dysfunction (n = 141; 12.9%), functional isolated TR (n = 89; 8.1%), organic TR (n = 53; 4.8%), and congenital causes (n = 18; 1.7%)[7]. Therefore functional TR is by far the most prevalent form of TR.

Prognostic implications of Tricuspid Regurgitation

The prognostic repercussions of TR have been a matter of debate during the years. An early publication by Braunwald et al.[3], published in 1967, advocated for conservative management of TR in patients undergoing MV surgery because it was felt that TR would improve or disappear after mitral treatment. After this study was published, the TV was named the "forgotten valve", and the most preferred approach was a conservative one.

In 2004, Nath et al. clearly demonstrated the negative effects of severe TR in contrast to the earlier study by Brunwald. In a consecutive series of 5223 patients undergoing echocardiography, these authors demonstrated a mortality increase corresponding to an increase in TR severity. After adjusting for age, left ventricle ejection fraction (LVEF), and RV size, survival independently increased in the presence of severe TR (hazard ratio [HR] 1.3, 95% confidence interval [CI] 1.05–1.66)[3]. This finding was supported by different contemporary natural history and outcome studies. Topilsky et al.[8] reported a population with idiopathic functional TR in which severe isolated TR independently predicted higher mortality, and 10-year survival was lower with an effective regurgitant orificae area (EROA) ≥ 40mm^2 versus < 40 mm^2. Prihadi et al.[9] used serial echocardiography to study significant TR development and reported a 42% mortality rate during a 2.9-year follow-up period.

In a recent analysis, Chorin et al.[3] demonstrated that 1-year mortality rates increased with increasing TR severity (7.7%, 16.8%, 29.5%, and 45.6% for patients with no, mild, moderate, and severe TR, respectively) with a multivariable analysis confirming the increase in the risk of death corresponding to increasing TR severity (Fig. 2). After adjustment for clinical and echocardiographical parameters (including age, gender, and other comorbidities in addition to multiple echocardiographical parameters), a Cox proportional hazards method showed that patients with moderate TR (HR 1.15, 95% CI 1.02–1.3; P = 0.024) and severe TR (hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.08–1.88; P = 0.011) had a worse 1-year prognosis when compared with no/minimal disease. Therefore, moderate TR was also identified as a significant independent predictor of mortality when compared with patients who had no or mild TR. Furthermore, re-hospitalization due to HF was also related to disease severity with a proportional hazard model showing an increase in the risk of re-hospitalization for moderate or severe TR in ambulatory patients and for severe TR in previously hospitalized patients.

Therefore, in view of recent studies supporting the association of TR with increased mortality, we can conclude that the presence of TVR is a negative prognostic predictor and that the TV should no longer be considered the “forgotten valve”.

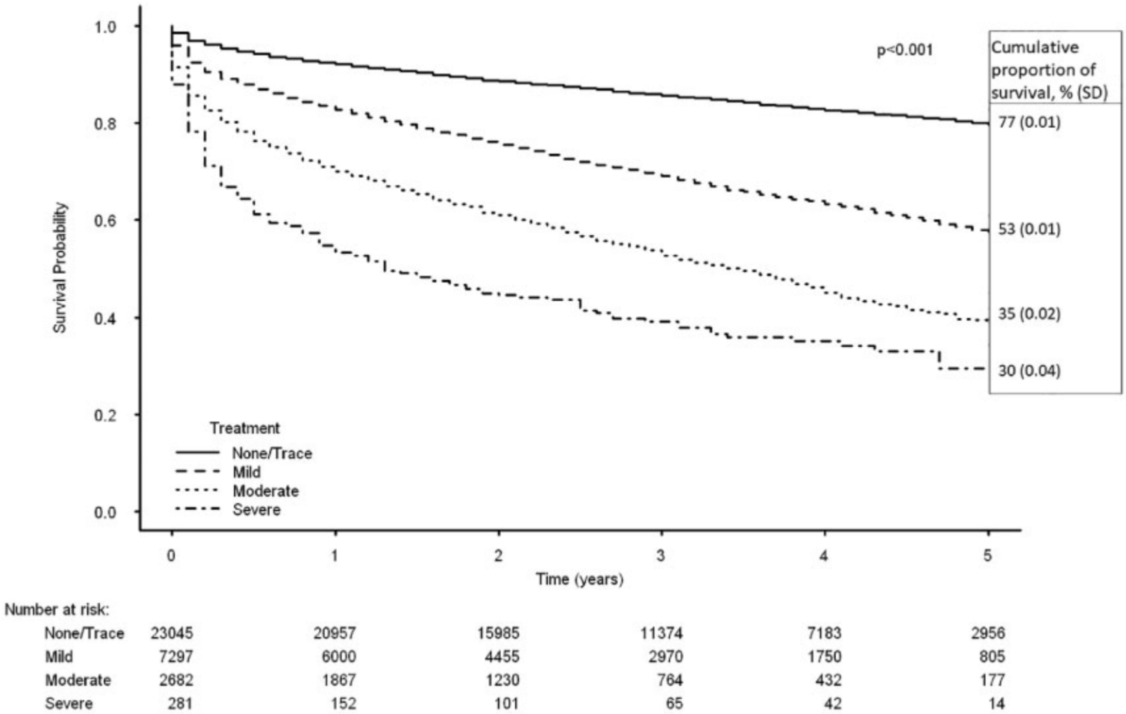

Figure 2. Kaplan–Meier survival curves according to tricuspid regurgitation (TR) grade. Chorin, E. et al. Tricuspid regurgitation and long-term clinical outcomes. Eur. Heart J. Cardiovasc. Imaging 21, 157–165 (2020).

Anatomy of the tricuspid valve

The tricuspid valve complex consists of the orifice of the valve and its associated annulus, cusps, supporting chordae tendineae (CT) of various types, and papillary muscles. The harmonious interplay of these structures together with the atrial and ventricular myocardium depends on the conducting tissue and the mechanical cohesion provided by the fibroelastic cardiac skeleton.

Although the TV has similar structures when compared with the MV , the TV also has its own specific characteristics. Its orifice is larger than the orifice of the MV, and the leaflets are thinner and more translucent than found in the MV. Although the TV is located at the atrioventricular border, a well-defined annulus fibrosus as seen in the mitral valve is not present in the TV. Both valves, however, have structural similarities. namely, the capability to open and close rapidly due to their remarkable mobility, which is also facilitated by the specific composition of chordae attachment at the leaflets and leaflet that is anchored in the annulus. The annulus, which undergoes three-dimensional (3D) changes in its area and has a specific gravity approximating that of blood, a smooth surface minimizing friction, and a large area of coaptation between the leaflets, contributes to this rapid mobility[10].

Annulus

The annulus is a fibromuscular ring that encircles the atrioventricular junction, marking the border between the atrial and the ventricular myocardium. The annulus connects the valve leaflets to the heart chambers. Some studies have found the TV annulus is predominantly saddle-shaped[11,12]. The configuration of the TV annulus plays a major role in the coaptation, mobility, and stress distribution in the leaflets and chordae tendineae[13]. The average diameter of the TV annulus in end-systole is 3.15 cm. As the annulus curvature increases, the stress in the TV anterior leaflet decreases, and this alteration in the curvature ultimately results in an increase in leaflet strain and abnormal tissue remodelling[14].

Structurally, the annulus coincides with the base of the TV leaflets and is composed of two types of discontinuous segments: 1) muscular annulus and 2) collagen-rich fibrous annulus. The muscular annulus is formed of a circumferentially-orientated myofibers lamina and a second lamina formed of myofibers perpendicular to the circumferential myofibers[15]. Racker et al[16] described that the anterior, lateral, and posterior region of the annulus are completely encircled with circumferential myofibers with only a thin muscular connection at the medial region of the TV annulus. The fibrous annulus forms the antero-medial regions and follows the connective tissues into the TV leaflets. Histological observations confirm the presence of the myofibers in the posterior and anterior annuli and collagen bundles in the septal annulus[17].

Leaflets

The annulus transitions in three leaflets known as the septal (TVSL), anterior (TVAL), and posterior (TVPL), are shown in Fig. 3.

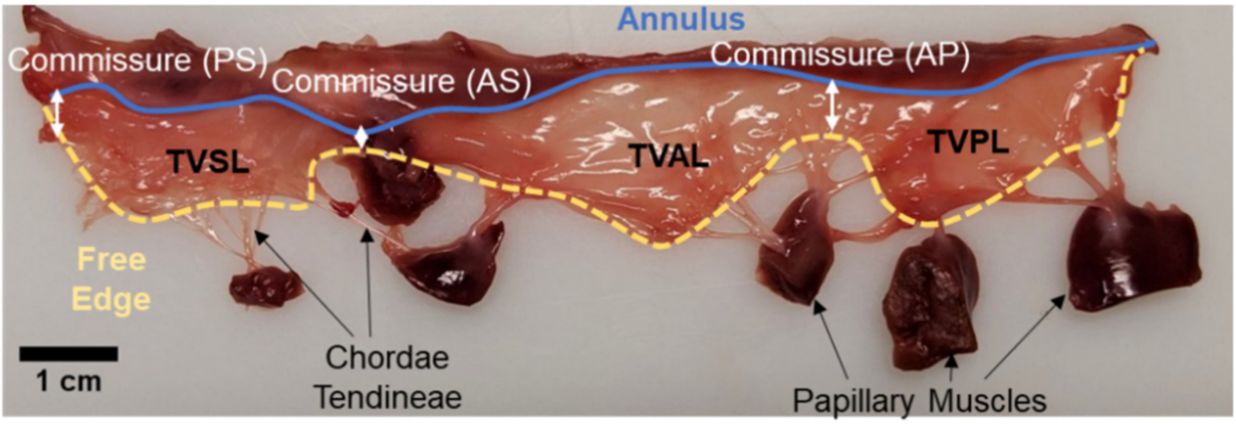

Figure 3. An excised porcine tricuspid valve (TV) tissue sample, showing the three TV leaflets, papillary muscle (PM), chordae tendineae (CT), commissures, and the TV annulus.

Normally, the leaflets have a rough zone at the free margin to which the CT are attached, a broad basal zone at the apex of the leaflet, and a clear zone. The three leaflets of the TV differ in size. The anterior leaflet is the largest. It stretches from the infundibular area downwards to the inferolateral wall of the right ventricle. The septal leaflet is attached to both the membranous and muscular portions of the ventricular septum. The posterior leaflet is the smallest and is attached to the tricuspid ring along its posteroinferior border. In a recent analysis of 100 autopsied hearts, Sakon et al.[18] demonstrated that the posterior leaflet can have different scallops and can be classified as a single, two, or three scallops. The proportion of the annulus increases proportionally in case of two or three scallops and accordingly, the anterior and septal annuli proportion significantly decrease from one to three posterior scallop leaflets. The TV leaflets normally have less collagen proteins when compared with the mitral valve, which results in a thinner and more translucent tissue[19].

Microscopic analysis has revealed that the layered structure of the TV and its composition of extra cellular matrix (ECM) proteins contain elastin, collagen, proteoglycans (PGs), and glycosaminoglycans (GAGs), populated with valvular interstitial cells (VICs). The connective tissue structure is organized into four morphologically and biomechanical distinct layers: 1) the atrialis (A), 2) spongiosa (S), 3) fibrosa (F), and 4) ventricularis (V)[20].

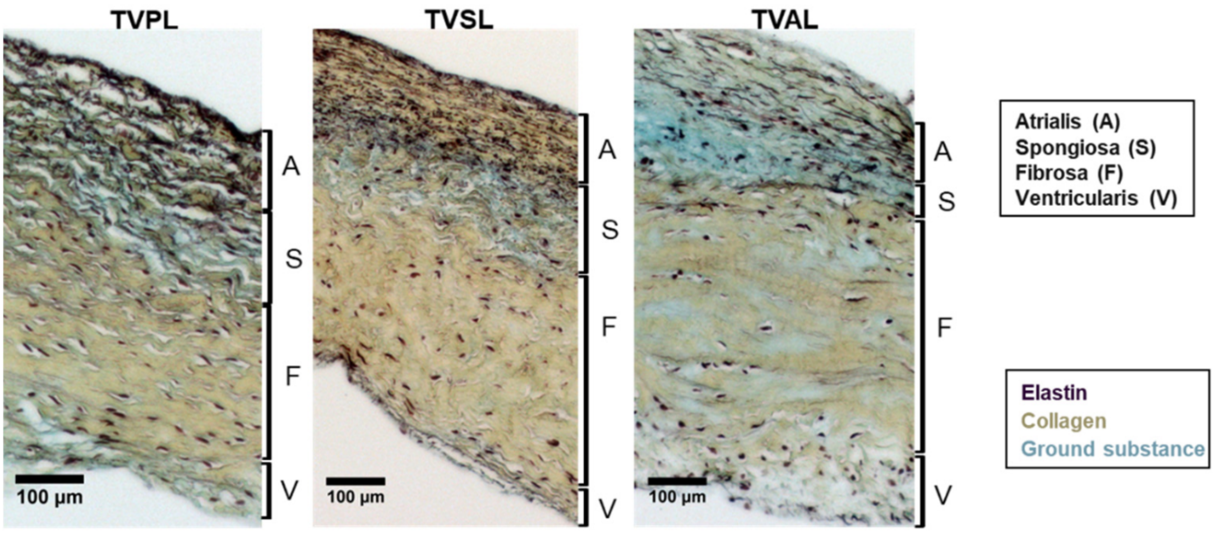

Figure 4. Histological images revealing the porcine TV leaflet microstructure using Movat's Pentachrome staining

to emphasize the elastin, collagen, and non-fibrous ground substance. The four morphological distinct layers are also illustrated in each image: 1) A: atrialis, 2) S: spongiosa, 3) F:fibrosa and 4) V: ventricularis.

The atrialis layer is composed of elastin, collagen, and glycosaminoglycans (GAGs) and is reported to have a high innervation density[21]. Further, valve interstitial cells (VICs) are heterogenous, dynamic cells that are distributed through the leaflets layers. These cells are interconnected in various ways. They show either straight borders that are interlocked with each other or 'roof tile'-like overlaps. It has been speculated that these arrangement is of importance to maintain the structural integrity under maximum stretch[22]. VICs play a major role in maintaining the structural integrity of the leaflet tissues via regulation of remodeling of the extracellular matrix (ECM) scaffold. Different VIC phenotypes express molecular markers found in myofibroblast and smooth muscle cells (SMCs). The activated VICs produce myofibroblasts and express smooth muscle α-actin in addition to other contractile proteins commonly found in the vascular SMCs . It has also been shown that the MV leaflet VICs are stiffer than the cells in the TV leaflets, implying a correlation between the VIC-regulated collagen biosynthesis and transvalvular pressure loading[23,24]. The spongiosa is composed of a loosely arranged layer of connective tissue; it is rich in hydrophilic GAGs and PGs, which act as dampening mechanism during rapid leaflet bending[25]. The lamina fibrosa is composed of dense collagenous fibres, which form a solid plane. Electron microscopic (EM) sections through the leaflets reveal the fibres are arranged in a parallel manner and are vertical to the free margins of the leaflet[22]. The ventricularis, which faces the ventricular side of the heart under the fibrosa, is rich in circumferentially-oriented elastin fibres that assist in stretching and recoiling of the valve tissue.

Chordae tendineae (CT)

The CT of the TV show a similar composition as the CT of the MV. CT are composed of elastin, GAGs, collagen fibers, and endothelial cells. The CT are typically categorized as basal, marginal, strut, or commissural as based on their leaflet attachment location. Each category is associated with varying lengths, cross-sectional areas, and mechanical properties of the CT. For example, the marginal chordae that are connected to the free edges of the leaflets are stiffer than the basal chordae that are attached to the TV annulus[26].

The distribution of different types of true and false chordae is depicted in Table 1. The most typical type of false chordae observed was the pillar wall (N = 10) followed by strut (N = 6) and inter-pillar (N = 2).

Types of chordae in the right ventricle

S. No.	True chordae			Total true chordae	False chordae
	Cusp	Cleft	Commissure		
1	10	2	2	14	0
2	10	3	1	14	2
3	5	3	1	9	1
4	7	5	3	15	0
5	7	5	3	15	1
6	9	4	4	17	4
7	4	6	3	13	3
8	5	6	3	14	0
9	10	3	3	16	4
10	7	5	3	15	3

Table 1. Distribution of the chordae of the right ventricle (RV).

Papillary muscle

The papillary muscles (PM) play a vital role in atrioventricular (AV) valve function and prevent ventricular overdistension. The anterior papillary muscle (APM) of the RV is the largest muscle. Posterior papillary muscle (PPM) is frequently bifurcate or trifurcate in shape. The PM and their CT regulate the closure of the AV valve during systole. The moderator band (MB), also known as the septomarginal trabeculae, extends from the right side of the ventricular septum to the base of anterior PM conveys the right branch of the atrioventricular bundle and is presumed to prevent the over-distention of the right ventricle[27]. The number, length, and shape of PMs are variable. Several authors have classified PMs based on their shapes and pattern, which is mainly based on the number of bases and apices.

In recent anatomical study of 10 human hearts, Hosapatna et al.[27] observed three different shapes of the classical PM according to the shape of the tip of the papillary muscle: 1) conical, 2) truncated, and 3) flat-topped. The variant patterns observed were bifurcate, trifurcate and bifid base, and single apex (Figure 5). The measurements of the PM showed that the septal muscle is usually the smallest PM (Table 2).

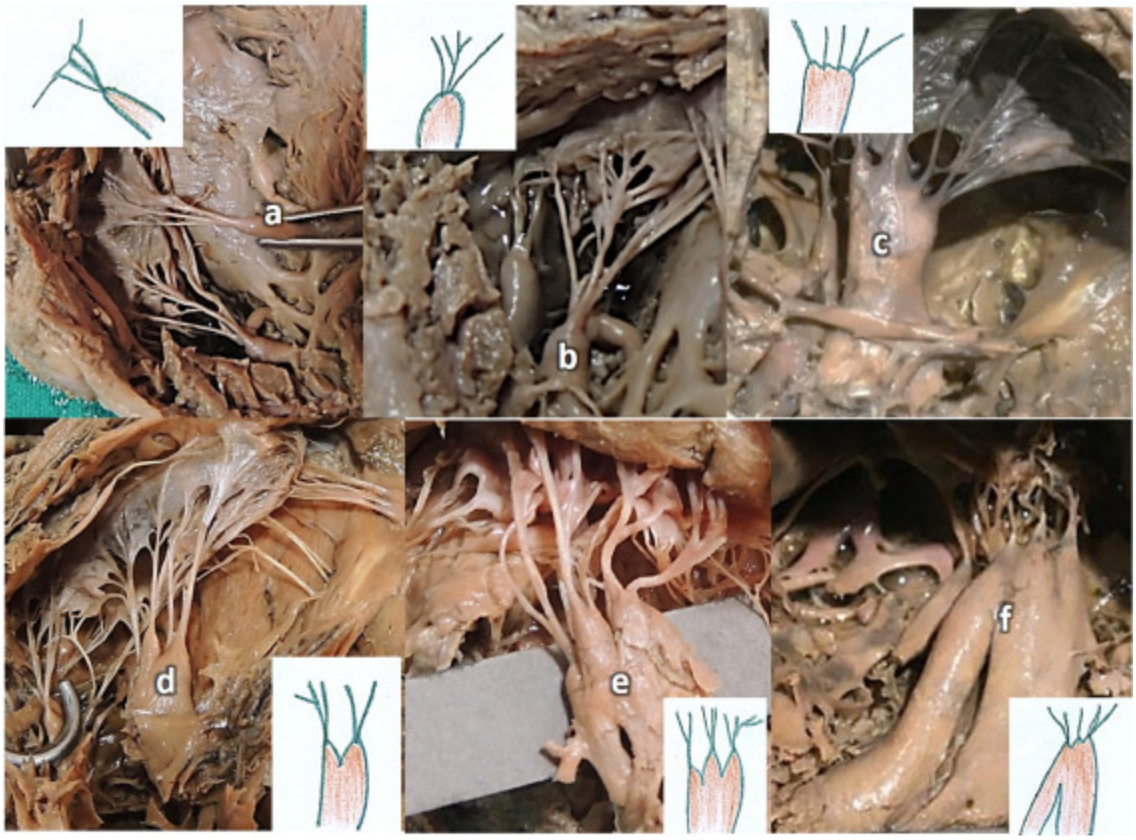

Figure 5. Cadaveric heart specimens along with schematic representations showing the opened ventricles with different shapes of papillary muscles:1) conical, 2) truncated, 3) flat-topped, 4) bifurcated, 5) trifurcated, and 6) separate base with a single apex.

Table 2. Dimension of the papillary muscle of the right ventricle.
Mean and standard deviation of the dimensions of the papillary muscles

Parameters measured in cm	Right ventricle		
	Anterior	Posterior	Septal
Length	1.43 ± 0.4	1.07 ± 0.5	0.38 ± 0.33
Breadth	0.58 ± 0.25	0.33 ± 0.1	0.25 ± 0.16
Ventricular wall thickness	0.42 ± 0.25	0.42 ± 0.22	NA

NA- Not Applicable

The anterior PM had 5.3 ± 1.9 chordae (range 3–8), the posterior PM had 2.7 ± 2.1 (range 1–6), and the septal PM had 3.5 ± 2.3 chordae (range 1–8) attached to them. Chordae from the APM was attached to both the anterior and posterior cusps of the tricuspid valve in five hearts. However, in the remaining five hearts, the chordae from the APM were attached only to the anterior cusp. In five hearts, the chordae from the PPM were found to be attached to the TV's anterior and posterior cusps. In three hearts, the chordae from the PPM attached only to the posterior cusp. However, chordae from the PPM were attached to the posterior and the septal cusps in the remaining two hearts. In seven hearts, the chordae from the septal PM was attached to the anterior and septal cusps of the tricuspid valve. In one specimen, the chordae from the septal PM was attached both to the posterior and septal cusps. However, the chordae from the septal PM was attached only to the septal cusp in the remaining two hearts. No chordae from the single PM were attached to any of the three cusps of the TV.

A study by Nigri et al. concerning the RVs revealed the absence of septal PM in 17 out of 79 hearts. This finding was confirmed by several authors with various percentages and incidences.

The variations in the morphological patterns of PMs can be attributed to their development. PMs develop from the trabecular myocardial ridge via the process of gradual delamination from the ventricular wall. If one or two PM fail to undergo delamination, this failure results in an asymmetry of the AV valve. Incomplete delamination of the trabecular ridge could be responsible for variations in the morphological characteristics of the PM[28].

Pathophysiology of functional tricuspid regurgitation

The aetiology of TR is generally classified according to the presence of an intrinsic TV abnormality (primary TR) and/or the presence of a right ventricular (RV) or right atrial enlargement leading to TA dilation and/or leaflet tethering (secondary or functional TR [FTR]).

Primary TR is caused by an organic process, which can be either congenital or acquired, that affects the valve or the subvalvular apparatus. Congenital TR can be attributed to an Ebstein anomaly in which the posterior and septal tricuspid leaflets are displaced apically in the right ventricle resulting in its atrialization. Rheumatic fever remains the most common cause of primary acquired TR worldwide and often presents with combined stenotic and regurgitant lesions and concomitant mitral valve disease. Another cause of primary TR in Western countries, wich occurs sometimes, is direct injury caused by implantable device leads that are associated with lead impingement on the leaflets, and/or papillary muscles and CT perforation, laceration, and/or transection[29]. TR is also a common manifestation of carcinoid syndrome, which affects the valves and endocardium of the right heart chambers. Less common causes of primary TR include chest wall or deceleration injury trauma, tricuspid prolapse due to myxomatous degeneration that is often associated with mitral valve prolapse, connective tissue disorders, systemic lupus erythematosus and/or rheumatoid arthritis complicated by marantic TV endocarditis, and drug-induced TR.

FTR develops due to structural alterations in right atrial and/or ventricular myocardial geometry and leads to TA dilation and/or leaflet tethering, both of which associated with impaired leaflet coaptation. This process is by far the most common cause of TR in adults as demonstrated by echocardiographic studies in which over than 90% patients with severe TR had a functional aetiology[30].

Multiple etiologies of FTR have been described:

- FTR is associated with LV dysfunction and/or left-sided heart disease, leading to left atrial dilation, an increase in pulmonary wedge pressure and RV afterload, and finally, post-capillary pulmonary hypertension (PH)[3].
- PH arising from other causes than left heart disease, such as primary PH, pulmonary embolism, and chronic pulmonary disease, can also cause TR due to an increase in RV afterload, RV dilation, and dysfunction [8].
- RV diseases, including isolated RV infarction or arrhythmogenic RV dysplasia, occurs less frequently [31] but can still lead to FTR.
- "Atriogenic" secondary TR is another often underappreciated but frequent cause of FTR. This condition is characterized by isolated atrial enlargement, usually in the presence of chronic atrial fibrillation, with normal RV size and morphology[32].

FTR is therefore not a valvular disease but rather an abnormality that results from a disease process that primarily affects the atrium or ventricle and subsequently alters the TA size and the mode of TV leaflet coaptation.

Coaptation is the area in which the leaflets come into contact during systole. A greater the coaptation corresponds to a smaller probability of regurgitation. A physiological coaptation occurs between the body of each leaflet and, hence, is called coaptation body-to-body. If, for any reason (TA dilation and/or leaflet tethering), the coaptation surface decreases, coaptation can then take place on the free edge of the leaflets, either symmetrically (edge-to-edge) or asymmetrically (edge-to-body). When significant TA dilation and/or leaflet tethering is present, no leaflet coaptation occurs at any stage of the cardiac cycle, thereby creating a single cavity between the RA and RV. Normal coaptation of the tricuspid leaflets during systole takes place either at the annular level or apically just below the TA plane with a good body-to body coaptation (around 5 to 10 mm of the leaflet bodies in contact with each other). The distance of the point of leaflet coaptation to the plane of TA can be measured and is referred to as the coaptation height. The area between the leaflets and the annular plane can be measured and is called the tethering area (Fig. 6).

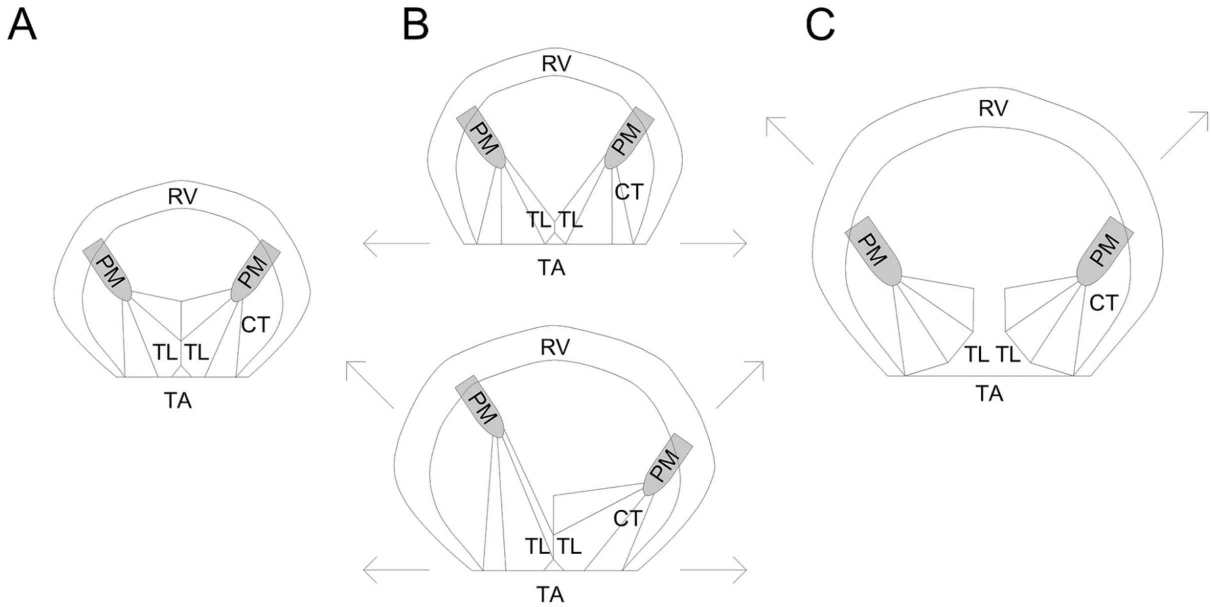

Figure 6. Schematic representation of the physiological and pathological modes of leaflet coaptation. (A) Physiological body-to-body coaptation. (B) Edge-to-edge leaflet coaptation (above); edge-to-body leaflet coaptation (below). (C) Lack of leaflet coaptation. CT, chordae tendineae; PM, papillary muscle; RV, right ventricle; TA, tricuspid annulus; TL, tricuspid leaflet. Etiology, epidemiology, pathophysiology and management of tricuspid regurgitation: an overview; Rev Cardiovasc Med. 2021 Dec 22;22(4):1115-1142.

Among patients with FTR, the mechanism leading to regurgitation differs between patients with PH or primary right ventricle dysfunction when compared with, for example, patients with atriogenic or atrial FTR. Recently, these two pathophysiological phenotypes were re-classified as ventricular forms of FTR (V-FTR) and atrial FTR (A-FTR)[3]. Using 3D echocardiography, Florescu et al. described a systematic comparison of the right chambers and TA geometry and function between patients with A-FTR and V-FTR with similar degrees of TR. They demonstrated that V-FTR patients have significantly abnormal RV diameters and volumes (all above Z score of 2) and a reduction in RV systolic function when compared with the controls. RV remodelling is consistent with a spherical or elliptical deformation with an increase in all diameter ratios and sphericity indioces; furthermore, TA dimensions and valvular tenting (expressed in tenting height and volume) were larger in V-FTR compared A-FTR. RV remodelling in A-FTR patients resembles a conical deformation shape, which is characterized by an increase in basal-to-mid and basal-to-longitudinal diameter ratios and a reduction in sphericity index (Fig. 7). Finally, the RA is dilated in both V-FTR and A-FTR with larger RA minimal volume in A-FTR and a larger TA in the V-FTR than in the A-FTR (Table 3).

	A-FTR	A-FTR controls	*P*-value	V-FTR	V-FTR controls	*P*-value
2D RV basal diameter index (mm/m^2)	24 ± 4	21 ± 3	<0.001	29 ± 5	20 ± 2	<0.001
2D RV mid diameter index (mm/m^2)	16 ± 4	16 ± 2	0.952	24 ± 6	15 ± 2	<0.001
2D RV length index (mm/m^2)	37 ± 5	37 ± 4	0.470	45 ± 6	37 ± 4	<0.001
2D basal-to-mid ratio	1.57 ± 0.2	1.37 ± 0.2	<0.001	1.26 ± 0.18	1.4 ± 0.2	<0.001
2D basal-to-length ratio	0.67 ± 0.1	0.57 ± 0.1	<0.001	0.66 ± 0.09	0.56 ± 0.1	<0.001
2D mid-to-length ratio	0.43 ± 0.1	0.42 ± 0.1	0.495	0.54 ± 0.11	0.4 ± 0.1	<0.001
2D sphericity index	43.3 ± 8.5	47.6 ± 7.8	0.011	61.84 ± 12.7	45.9 ± 8.4	<0.001
3D RV basal diameter index (mm/m^2)	27 ± 4	26 ± 3	0.106	36 ± 6	25 ± 3	<0.001
3D RV mid diameter index (mm/m^2)	21 ± 4	22 ± 3	0.155	36 ± 7	21 ± 3	<0.001
3D RV length index (mm/m^2)	41 ± 5	44 ± 4	0.001	54 ± 7	45 ± 4	<0.001
3D basal-to-mid ratio	1.33 ± 0.1	1.21 ± 0.1	<0.001	1.13 ± 0.1	1.23 ± 0.1	<0.001
3D basal-to-length ratio	0.68 ± 0.1	0.6 ± 0.1	<0.001	0.67 ± 0.1	0.57 ± 0.1	<0.001
3D mid-to-length ratio	0.51 ± 0.1	0.5 ± 0.1	0.286	0.6 ± 0.1	0.47 ± 0.1	<0.001
3D sphericity index	56.3 ± 8.4	62.9 ± 9	<0.001	81.9 ± 12.8	62.8 ± 8.8	<0.001
RV end-diastolic volume index (mL/m^2)	62 ± 16	57 ± 10	0.045	113 ± 41	57 ± 11	<0.001
RV end-systolic volume index (mL/m^2)	30 ± 10	23 ± 6	<0.001	65 ± 30	23 ± 6	<0.001
RV ejection fraction (%)	51 ± 6	60 ± 5	<0.001	45 ± 9	59 ± 6	<0.001
RV free-wall longitudinal strain (%)	23 ± 5	28 ± 4	<0.001	17 ± 8	28 ± 3	<0.001
TAPSE (mm)	20 ± 4	24 ± 4	<0.001	18 ± 6	24 ± 4	<0.001
3D RA maximum volume index (mL/m^2)	60 ± 28	28 ± 6	<0.001	54 ± 21	28 ± 6	<0.001
3D RA minimum volume index (mL/m^2)	48 ± 26	13 ± 4	<0.001	32 ± 19	12 ± 4	<0.001
2D RA maximum volume index (mL/m^2)	53 ± 24	24 ± 6	<0.001	55 ± 24	23 ± 6	<0.001

2D, two-dimensional; 3D, three-dimensional; A-FTR, atrial functional tricuspid regurgitation; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; V-FTR, ventricular functional tricuspid regurgitation.

Table 3. Comparison of right ventricular (RV) and right atrial (RA)size and function between patients with the atrial and ventricular phenotype of functional tricuspid regurgitation (FTR) and their respective controls; European Heart Journal - Cardiovascular Imaging (2022) 23, 930–940.

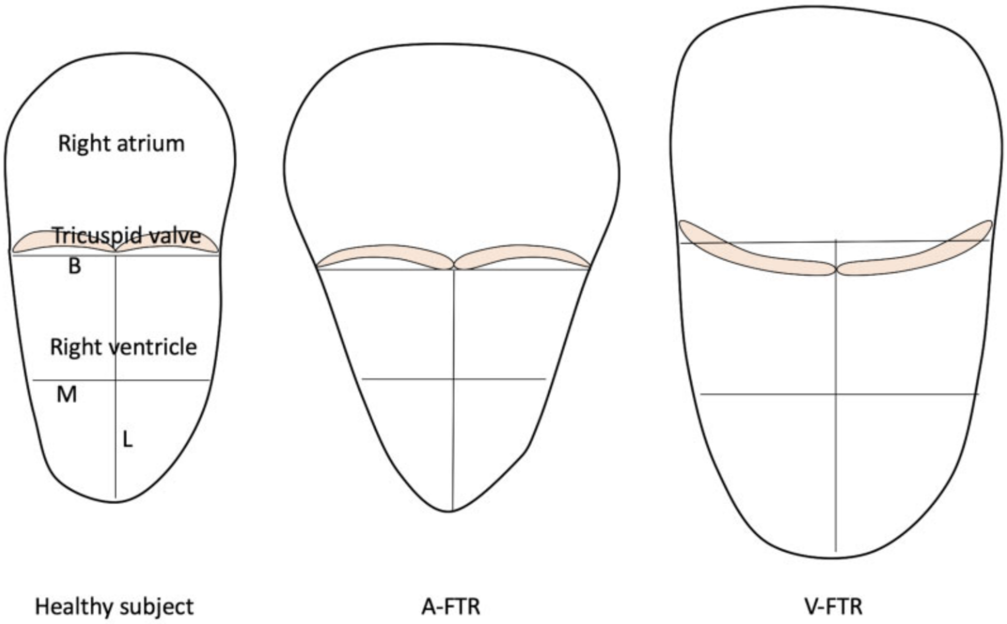

Figure 7. Morphological alteration of the atrial and ventricular forms of tricuspid regurgitation (A-FTR and V-FTR, respectively) in the right atrium (RA) and RV, basal (B) diameter, mid diameter (M) and longitudinal diameter (L). Right heart chamber geometry and function in patients with A-FTR and V-FTR; European Heart Journal - Cardiovascular Imaging (2022) 23, 930–940.

The ventricular remodelling in the V-FTR has a direct effect on the papillary muscle position. Studies using 3D echocardiography[3] and computed tomography imaging (CTI) [33] identified displacement of posterior and anterior PMs, laterally and apically. respectively, and this displacement increased with a higher degree of FTR. Furthermore, the authors demonstrated that in cases of dilatation of the RV and LV, the displacements were predominantly apical, while in the case of isolated RV dilatation. the displacement occurred apically and away from the centre of the RV (Figure 8). Therefore, in PH of the V-FTR phenotype, TR appears only when the dilatation of the ventricle is enough to displace the PM and induce tethering of the leaflets and reduction of their coaptation.

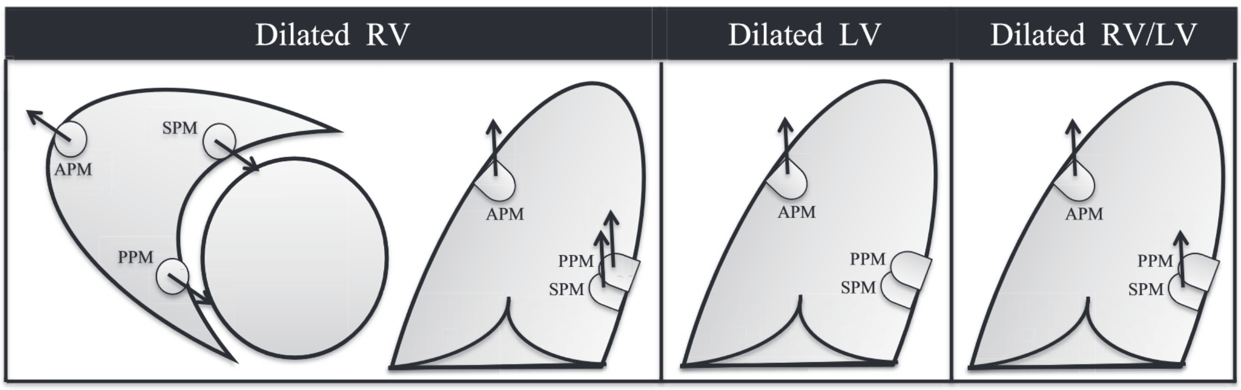

Figure 8. Depiction of significant differences in PM displacement for all classifications when compared with the control. Patients with a dilated RV had significant displacement of all PMs apically and away from the center of the RVs. Patients with a dilated left ventricle (LV) had significant displacement of the anterior PM towards the apex. Patients with both RV and LV dilatation had significant apical displacement of the APM and PPM muscle.

This finding was also indirectly demonstrated using an animal model of acute PH [34]. After pulmonary artery external occlusion, the authors demonstrated a volume increase in the RV in addition to TA dilatation, but none of the sheep developed significant TR despite RV distension. The lack of TR may be the result of a compensatory mechanism involving annular contractility, lack of chronic pressure overload, and ventricular and annular remodelling. In that study, the decrease in annular contractility was in the range of 3% to 4%, which perhaps was insufficient to make the valve incompetent. Moreover, the 25% increase in RV pressure was inadequate to induce TR when compared with another study in which a 66% RV volume increase was associated with moderate/severe TR in 60% of the studied animals[35].

Tricuspid annulus alteration also has a crucial role in FTR development. In both phenotypes A- and V-FTR, the annulus is dilated with Z score above the 2 (see Table 4).

Z-scores	**A-FTR**	**V-FTR**	***P*-value**
2D RV basal diameter index	1.2 ± 1.5	3.9 ± 2.2	<0.001
2D RV mid diameter index	0.1 ± 1.5	4.0 ± 2.5	<0.001
2D RV length index	-0.2 ± 1.3	2.1 ± 1.5	<0.001
3D RV basal diameter index	0.4 ± 1.3	4.1 ± 2.3	<0.001
3D RV mid diameter index	-0.3 ± 1.3	3.8 ± 2.4	<0.001
3D RV length index	-0.8 ± 1.1	2.3 ± 1.8	<0.001
RV end-diastolic volume index	0.6 ± 1.6	5.3 ± 3.8	<0.001
RV end-systolic volume index	1.3 ± 1.8	7.1 ± 5.2	<0.001
RV ejection fraction	-1.6 ± 1.2	-2.6 ± 1.7	<0.001
3D RA maximum volume index	5.4 ± 4.8	4.4 ± 3.5	0.2
3D RA minimum volume index	9.4 ± 7	5.5 ± 5.1	0.001
2D RA maximum volume index	4.7 ± 4	5.7 ± 4.4	0.214
TA 3D mid-systolic area	2.4 ± 1.3	4.4 ± 3.4	<0.001
TA 3D end-diastolic area	2.4 ± 1.7	3.7 ± 3.3	0.01

2D, two-dimensional; 3D, three-dimensional; RA, right atrium; RV, right ventricle; TA, tricuspid annulus.

Table 4. Comparison of the Z-scores of the echocardiographic parameters describing RV, RA, and tricuspid annulus geometry and function between patients with A- and V-FTR. Right heart chamber geometry and function in patients with the A- and V-FTR regurgitation; European Heart Journal - Cardiovascular Imaging (2022) 23, 930–940.

In a normal heart, the tricuspid annulus is saddle-shaped with a non-planar structure and a distinct bimodal or saddle-shaped pattern having two high points (oriented superiorly towards the RA) and two low points (oriented inferiorly towards the RV) as shown in Figure 9.

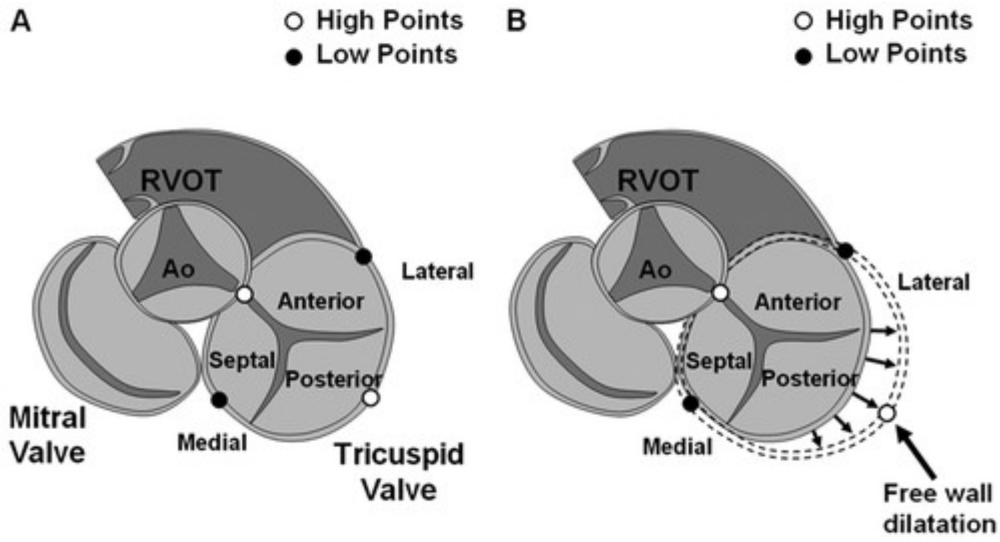

Figure 9. A, TV viewed from the atrium. The valve relative to anatomic structures is displayed, demonstrating the location of high and low points. B, Dilation along the free wall aspect of the TV with FTR (dashed lines). The RVOT represents the RV outflow tract; Ao, aorta.

On a 3D echocardiography analysis, Ton-Nu et al.[3] examined the TA in patients with at least moderate FTR and compared this FTR with two reference groups: 1) one (reference I) consisted of patients with normal TV function (morphologically normal tricuspid leaflets with no or trace TR) and without structural heart disease and 2) the second reference group consisted of patients with normal TV function but who had either left ventricular (LV) dysfunction, mitral valve disease, or pulmonary hypertension. They found that the bimodal pattern of the TA was consistently observed in all reference subjects. In patients with functional TR, the annular area was larger, and the tricuspid annulus was flatter, which led to a decreae in the the saddle shape. When compared with the reference groups, patients with functional TR had greater percentage increases in the antero–posterior (A–P) distance (88%) than in the medial–lateral (M–L) distance (31%), a finding that is consistent with greater dilation along the free-wall aspect of the annulus. In addition, the annulus became more circular with a decrease in the M–L to A–P ratio.

Two types of annular shapes with functional TR were noted and were termed “intermediate” and “advanced.” Both shapes were within the spectrum of becoming more planar relative to the reference groups. The intermediate shape had one distinct high point located anteriorly with the posterior edge becoming flat relative to the anterior high point (Fig 10, B). The advanced shape was more uniformly flat in both the anterior and posterior locations (Fig 10, C). The H–L distances of the tricuspid annulus are displayed for reference, intermediate, and advanced shapes in the corresponding bottom panels of Fig 10 F. Both intermediate and advanced annular shapes were more dilated, planar, and circular relative to the reference groups (Figure 10).

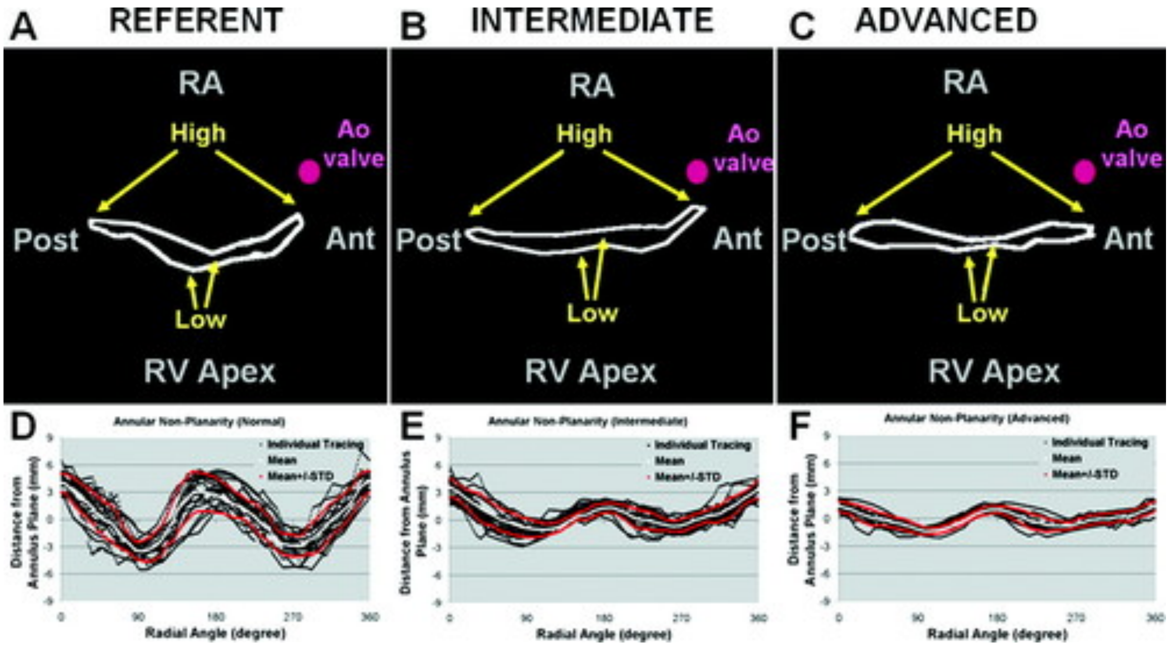

Figure 10 Top, TA viewed from a profile displaying anteroposterior view. A, Reference patient with two high points located anteroposteriorly. B, Intermediate shape in patient with functional TR with only one high point located anteriorly. C, Advanced shape in patient with functional TR with no distinct high point. Ant indicates anterior; Ao valve, aortic valve; Post, posterior; and RA, right atrium. Bottom, Tracings of the TA displayed as a function of radial angle and the height (distance of annular points from the least-squares plane): D, referent; E, intermediate; and F, advanced. STD indicates standard deviation.

Furthermore, these data were corroborated by the significant correlation between the TV annulus area and the loss in saddle shape as shown in the next figure and were consistent with the observation that as the TV annular area dilates, it becomes more planar and loses its bimodal shape (Fig 10).

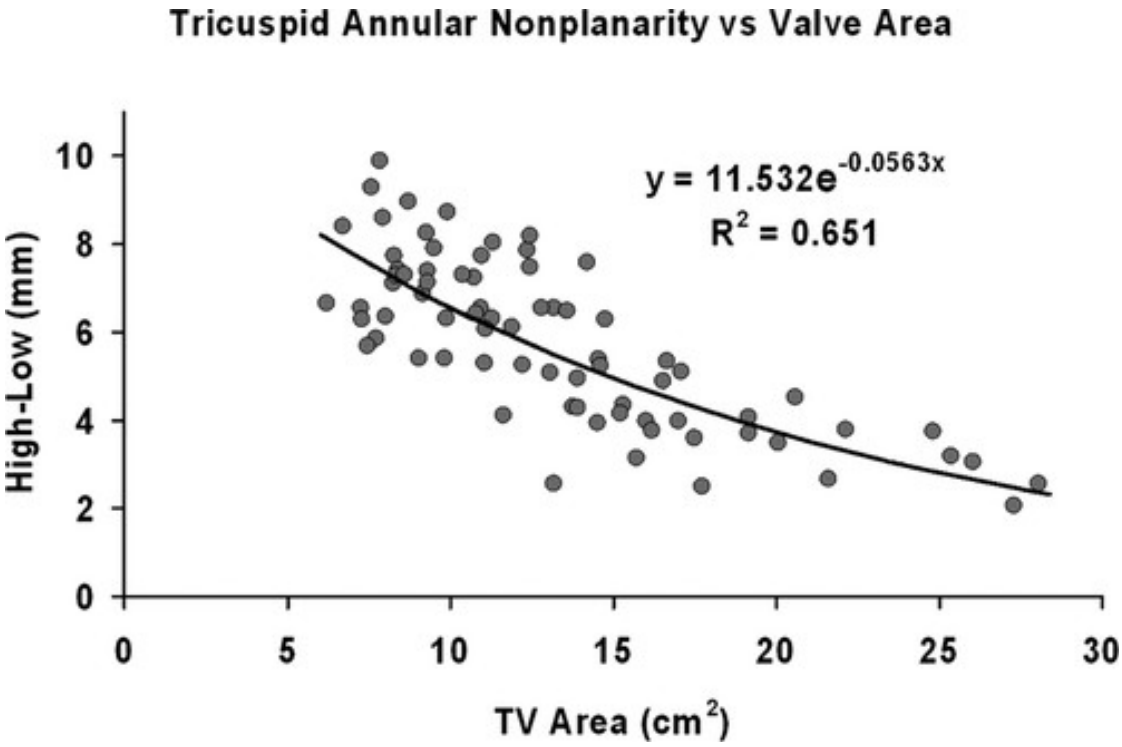

Figure 11. Inverse and continuous relationship between TA area and degree of planarity (H–L distance). Geometric Determinants of Functional Tricuspid Regurgitation. Insights From 3-Dimensional Echocardiography. Circulation. 2006;114:143–149.

Furthermore, not only the shape and dimension of the TA changed, but the regional contractility also decreased. In an ovine model of PH[34], the anterior region decreased significantly its contractility decreased significantly (17% ± 7% versus 14% ± 8%; P =0.02). However, its pericommissural segment (near the antero-posterior commissure) was most affected by PH with a decrease in its contractility from 15% ± 7% to 11% ± 7% (P = 0.04). A trend towards a decrease in contractility of the posterior region with PH was found (14% ± 8% versus 11% ± 6%; P = 0.058).

FTR development also depends on the relationship between the leaflet and annulus area. Using a 3D echocardiography analysis , Afilalo et al.[36], demonstrated that the TV leaflet area plays a significant role in the appearance of FTR. The open tricuspid leaflets were traced during mid-diastole on successive rotational long-axis planes and reconstructed to obtain the tricuspid leaflet (TL) area (because the leaflet tissue overlaps at the coaptation point, tracing in systole is less accurate and is affected by systolic leaflet stretch). They also represented the tricuspid closure area during mid-systole as the leaflet area separating the RV and RA that would be necessary to occlude the tricuspid orifice as required by annular and ventricular tethering. The ratio of the TL area to tricuspid closure area was the primary predictor variable. A reduction in this ratio represented small valve leaflet decrease relative to a large annulus and tented closure area, which leads to valvular insufficiency (Figure 12).

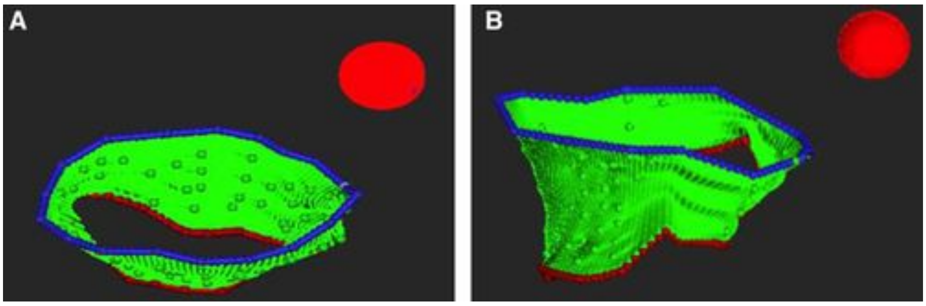

Figure 12. Three-dimensional (3D) rendering of open TL area. To generate these 3D models, the tricuspid leaflets were manually traced in the open position on successive rotational long-axis planes and then reconstructed. Leaflet Area as a Determinant of Tricuspid Regurgitation Severity in Patients With Pulmonary Hypertension. Cardiovascular Imaging. 2015;8:e002714

In patients with PH, the TV area increased by 46% when compared with the control group (median, 21.4 cm^2 versus 14.4 cm^2; $P < 0.001$). Despite the increase in RV volume and annulus area in patients with worsening TR a slight decrease in TLA from 22.5 cm^2 in patients with mild TR to 20.6 cm^2 in patients with severe TR. The ratio of TL area/closure area was inversely correlated with the vena contracta (VC) width (Figure 13). Specifically, the ratio of TL area/closure area was 2.09, 1.87, and 1.34 in patients with mild, moderate, and severe TR, respectively (Spearman R, −0.66; P < 0.0001).

When the TL area was inadequate to cover the closure area, a graded increase in TR severity was observed. The ratio of TL Area:closure area reflects the balance between leaflet adaptation versus annular dilation and tethering geometry and has proven to be a strong indicator of functional TR severity.

This finding is consistent with recent work on leaflet adaptation in functional MR. When compared with normal controls, patients with dilated cardiomyopathy or inferior wall motion abnormalities had a 35% increase in mitral leaflet area[37]. Interestingly, the biological mechanism for increased leaflet area was shown in a sheep model in which mechanical leaflet tethering/stress caused by PM retraction reactivated embryonic pathways associated with leaflet growth[38].

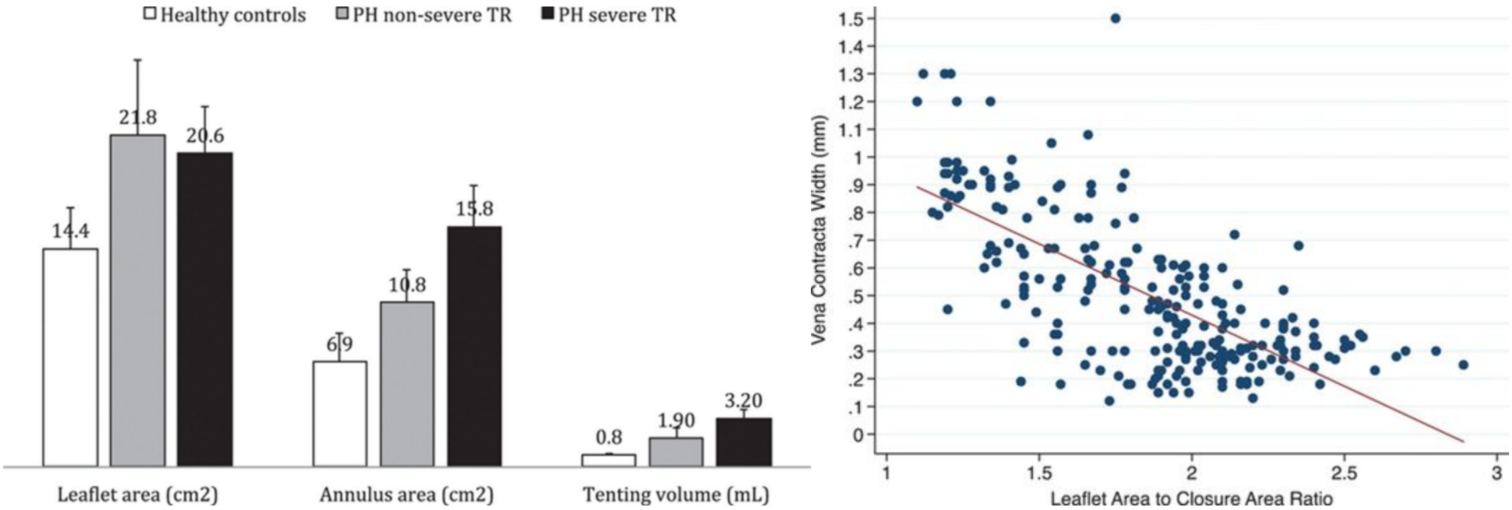

Figure 13. Left panel: TL area, annulus area, and tenting volume in the three groups. Right panel: Leaflet area:closure area ratio was inversely correlated with tricuspid regurgitation severity as measured by vena contracta width ($R = -0.66$; $P < 0.0001$).

Multimodality diagnosis of Functional TR

High-resolution imaging modalities have greatly helped to advance our understanding of TR and other cardiac abnormalities. Non-invasive imaging techniques used to assess TR include computed tomography imaging (CTI), cardiac magnetic resonance imaging (CMRI), and echocardiography. Echocardiography is most frequently used for diagnosing FTR, but CMRI and CT are selected more frequently as a complementary method. Clinicians use these advanced imaging techniques as a surgical intervention timing-indicator and for pre-operative surgery planning.

Echocardiography

Echocardiography, an imaging technique that uses ultrasound waves to image anatomical structures, is the principal modality used to diagnose TR. In the clinic, physicians assess pre-, intra-, and post-operative states of TR generally by two-dimensional 2D echocardiography. Echocardiography is relatively inexpensive, widely available, and capable of evaluating the TV both functionally and morphologically. This technique can be performed at a patient's bedside, so it is popular for imaging hemodynamically unstable patients. However, the operator-dependent interface causes certain restrictions. Two major methods exist for performing both 2DE and 3DE echocardiography: i) transthoracic echocardiography (TTE) and ii) transesophageal echocardiography (TEE). For TTE, the transducer probe is positioned noninvasively over the heart. Conversely, in TEE, the probe is inserted into the esophagus to access the heart more directly. While TTE continues to be the cornerstone of diagnostic cardiac ultrasound, TEE offers value as a supplementary tool due to the close probe proximity, decreased signal attenuation, and absence of impedance from intervening lung and bones. (Figure 14)

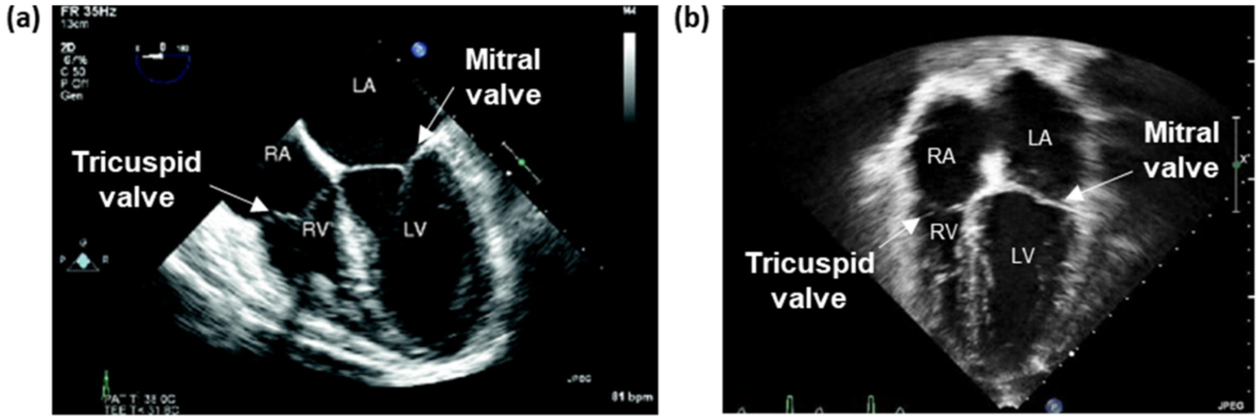

Figure 14 Echocardiographic imaging modalities: (a) a four-chamber mid-esophageal view using transesophogeal echocardiography (TEE) with image modified from [58] and (b) an apical four-chamber view (A4C) using transthoracic echocardiography (TTE).

<u>Standardard Echocardiography Imaging Windows</u>

Due to the complex, multi-component structure of the TV, 2D echocardiography requires acquisition of images from multiple locations to capture the valve's overall 3D geometry and function comprehensively. Using TEE, the right side of the heart is viewed from the mid-esophageal ([ME] 30–40 cm) or transgastric (40–45 cm) windows. The views generally used to image the TV include the right ventricular inflow-outflow ME and four-chamber ME as shown in Figure 14a (transducer angle: 0–20° and 60–90°, respectively) and the basal short axis and RV-inflow transgastric views (transducer angle: 0–20° and 100–120°, respectively). Also notable in assessing FTR are the views that delineate the RA and RV.

The traditional approaches for TTE include right ventricular inflow (RVIF), parasternal short-axis (PSAX), parasternal long-axis (PLAX) as shown in Figure 5a, apical four-chamber (A4C) as shown in Figures 4b and 5b, and more recently, right ventricular-focused (RVF). Addetia et al.[39] analyzed the efficacy of these traditional views compared to six nonstandard 2D views devised by their group. Using multiplanar reconstruction of 3D data sets, they showed that their novel 2D views accurately identify the TV leaflets based on defined landmarks and anatomical clues. Such nonconventional imaging protocols may be beneficial for further evaluating TV leaflet pathologies.

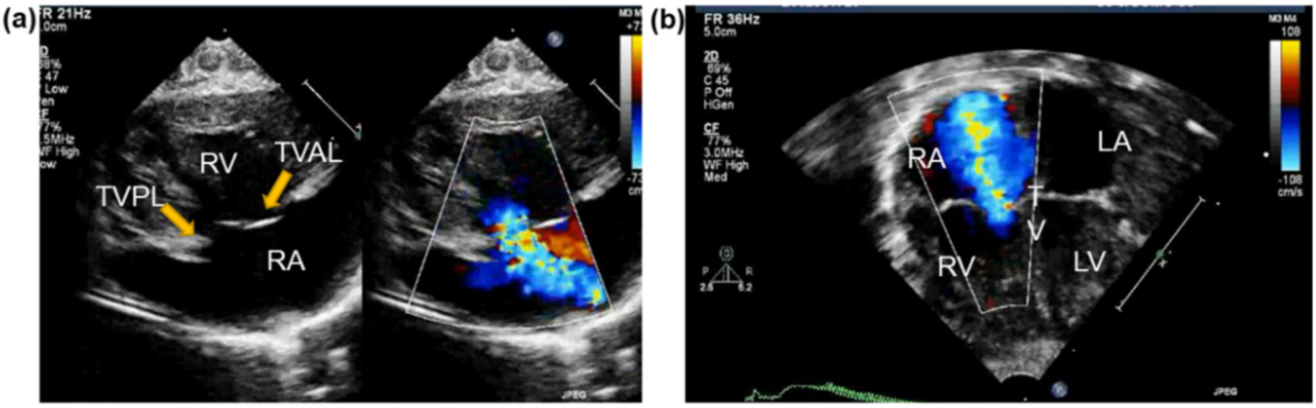

Figure 15. Visualization of severe TR using two different 2DTTE views and color flow Doppler: (a) a parasternal long-axis inflow view, and (b) an apical four-chamber view of a newborn with a severe pulmonary hypertension (PH) due to diaphragmatic hernia.

Three-dimensional imaging modalities

Unlike the MV or AV, the complex, nonplanar structure of the TV makes it nearly impossible to simultaneously capture the three TV leaflets in one cross-sectional view using only 2DE imaging. capturing the three TV leaflets in one cross-sectional view nearly impossible using only 2DE imaging. Real-time three-dimensional echocardiography (RT3D ECHO) supplements 2D echo with detailed anatomical measurements in 90% of patients[3], and allows for concurrent visualization of the opening and coaptation of the three leaflets through the cardiac cycle[40]. Moreover, in a comparison of 2D TTE and RT3DE, Anwar et al. [41]concluded that RT3D echo was more reliable for assessing the TA annulus) size and function.

3DE acquires volume data via transducer probes containing a special matrix array of 2500 piezoelectric crystals that can be independently activated, focused, and steered to scan a pyramidal volume of tissue in three dimensions[42]. In addition to the live RT mode, the 3DE transducer can also obtain full-volume data, which involves merging of information over four consecutive cardiac cycles using a wide angle to cover a larger region of interest (ROI). This process allows a practitioner to concurrently view both AV valves. However, full-volume imaging possesses limitations in terms of poor images and spatial resolution due to physiologically-based artifacts. Additionally, the need to suspend respiration for four cardiac cycles during imaging excludes patients with AF or dyspnea.

The three main RT3DE imaging views are parasternal, apical, and subcostal. In selecting one of these views, it is important to consider the response of an imaging system to a point object, known as the point-spread function of the system, which varies in degree according to the system dimensions in use. Standard RT3DE systems employ a dimension of approximately 0.5 mm (axial), 2.5 mm (lateral), and 3 mm (elevation), and thus, the best images (those with the least distortion and/or blurring) are acquired in the axial dimension. Conversely, the elevation dimension produces the greatest degree of spreading .

Evaluation and quantification of FTR

The echocardiographic analysis permits a qualitative, quantitative, or semi-quantitative evaluation of TR. Such analysis allows the classification of FTR in different degrees. Several parameters and techniques can be used.

Color Doppler jet area: the degree of TR has been graded for several years using the jet area (planimetry of maximal jet area in cm^2). Conventional guides use the thresholds of an area of >10 cm^2 to be severe. However the color jet area have several limitations. The most important physical factor determining color Doppler size is the momentum. Jet flow is governed by the conservation of the momentum (M), which is defined as flow (Q) multiplied by velocity (v) or effective regurgitant orifice area (EROA) x v^2. Thus for the same EROA, the jet area for a TR jet (Figure 16 panel A) may be one-fourth the area of a MR jet (Figure 16 panel B).

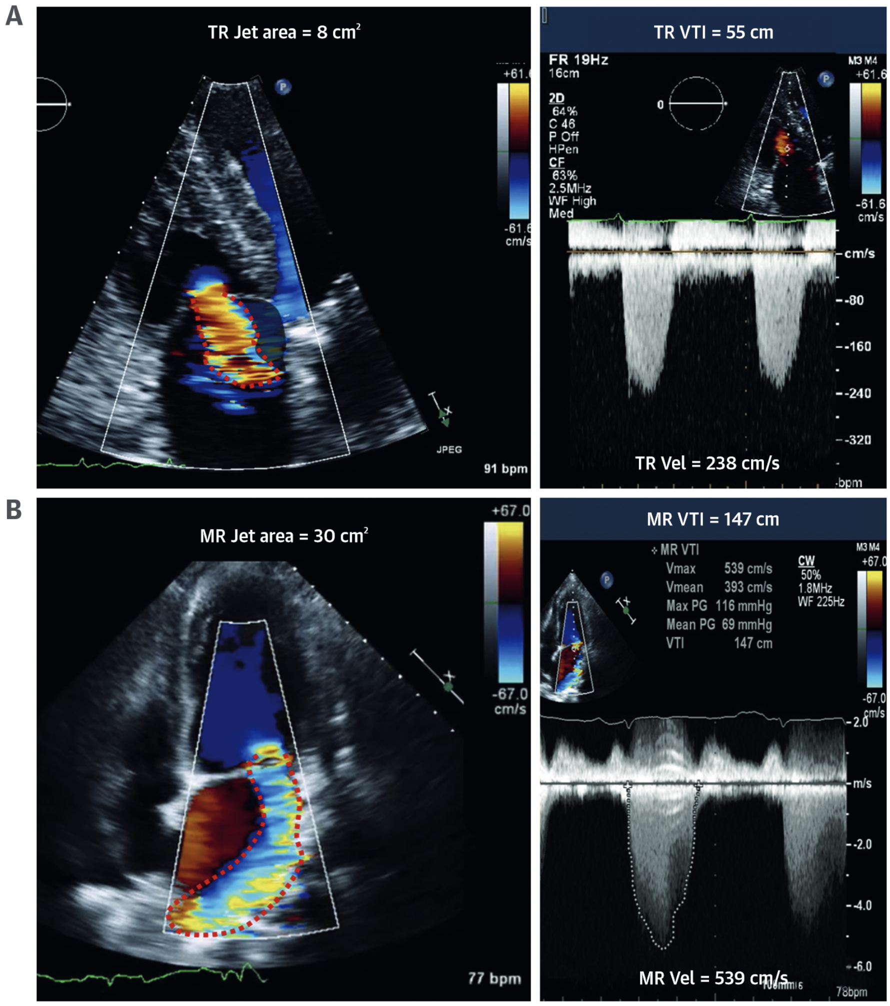

Figure 16. The same effective regurgitant orifice area (EROA), the jet area (red dotted outline) for a TR jet (A) may be one-fourth the area of a mitral regurgitant jet (B). In these examples, the EROA for both regurgitant jets is ~55 to 60 mm^2. The MR jet area is much larger than the TR jet area but may be restricted by the eccentric, wall jet. CW = continuous wave; EROA = effective regurgitant orifice area; MR = mitral regurgitation; PG = pressure gradient; TR = tricuspid regurgitation; Vel = velocity; VTI = velocity time integral.

Reducing the scale also reduces the minimal velocity that can be depicted, which causes the jet area to appear larger. Regurgitant jets can be reduced in size due to constraints on the chamber, especially a constraint into an adjacent wall. For these limitations and drawbacks, the European Association for Echocardiography does not recommend the use of the regurgitant jet area to grade TR[43].

Vena contracta width: a semiquantitative way to measure TR simply uses the width of the color jet at its narrowest point as it passes through the VC. The 2017 American Society of Echocardiography valve regurgitation guideline suggests that a VC width < 3 mm indicates mild TR, whereas a VC width > 7 mm indicates severe TR. The noncircular and nonplanar shape of the regurgitant TR orifice results in highly variable VC measurements depending on the imaging plane. Further, VC widths are influenced by poor lateral resolution, flow rate, and machine settings. *In vitro* studies have demonstrated that VC width obtained by color Doppler can be more than double the size of directly visualized orifices[44]. 3D color Doppler studies have indicated that the VC cross-sectional shape is often ellipsoidal or crescent-shaped with a long anterioposterior direction [45](Figure 17).

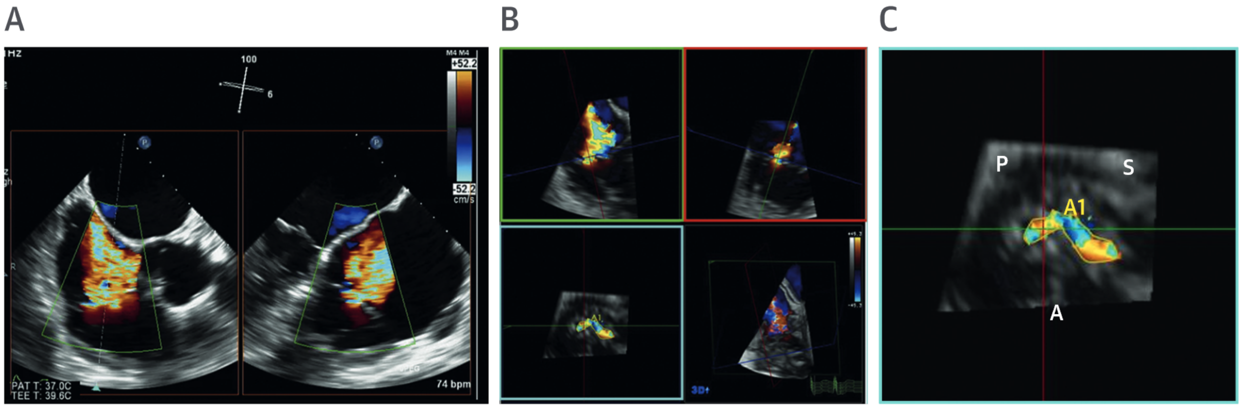

Figure 17. Because the shape of the TR jet is frequently irregular, the vena contracta (VC) diameters vary based on the imaging window. (A) Simultaneous multiplane imaging shows different VC diameters. The 3D color Doppler image (B) aligns the green and red planes to image the VC in the blue plane. (C) The blue plane with S, P, and A leaflets with the regurgitant jet between both the A–S and A–P commissures. A = anterior leaflets; P = posterior leaflets; S = septal leaflets;

VC width demonstrates a prognostic significance with a threshold of > 7 mm as measured from a single 4-chamber view predictive of cardiovascular events with an hazard ratio (HR) of 1.72[46].

Proximal Isovelocity Surface Area (PISA) method: the proximal convergence zone on the RV side is normally laminar with smoothly accelerating flow as the regurgitant orifice is approached and this blood has a hemispheric isovelocity shells of increasing velocity and decreasing surface. For a contour with velocity, v_a, at the radius from the orifice, the flow rate Q is given by $Q = 2\pi r^2 v_a$. This contour can be identified by reducing the aliasing velocity until the red–blue line contour is measured and appears roughly hemispherical. Once Q is known, using the conservation of the mass principle, the EROA is given by Q/V_{max}, in which V_{max} is the maximal velocity obtained from the continuous wave (CW) Doppler through the jet at the time of the proximal isovelocity surface area (PISA) radius measurement. Multiplying this orifice area by the time–velocity interval of the CW Doppler tracing should than yield the regurgitant volume. The major limitations are the elliptical shape of the regurgitant orifice in FTR with the largest diameter in the antero-posterior direction. Therefore, the PISA generated by this orifice result to be hemi-elliptical rather than hemispheric[45]. Second, the FTR may vary over time; thus, a single PISA measurement may not adequately represent the regurgitant orifice over the systolic interval. Studies comparing the PISA method to quantitative EROA demonstrated an underestimation of TR severity up to 40%. This underestimation is due to the fact that the tethered tricuspid leaflet will result in a proximal jet extent that is greater than a hemisphere, which results is a smaller PISA radius. Correcting for the angle of the leaflets causes a. change in the correlation between the calculated TR and the quantitative Doppler method[47]. The use of 3D color Doppler PISA has also demonstrated a possible improvement in the TR quantification with a very high correlation with 3D plani-metered VC area (r = 0.97)[48] as shown in Figure 18.

Volumetric quantification: this method has been considered an optimal approach to any regurgitant lesion. This method compares the stroke volume going through the regurgitant valve (the diastolic forward volume across the TV) with a reference stroke volume from a region of the heart without regurgitation of shunting (such as the LV outflow tract). This method can be utilized in the presence of multiple jets or irregular shape orifices. Normally a single plane tricuspid annular diameter is taken from the 4-chamber view and the pulsed-waved (PW) Doppler sample volume for measuring the velocity time integral (VTI) was placed at the tips of the leaflets. An improvement in this technique involves the use of two orthogonal plane annular diameter values in early diastole in the formula for an ellipse that may be more accurate for the annular area. The orthogonal plane can be measured using the inflow and 4-chamber views or a simultaneous biplane image of the annulus[49]. The tricuspid annular VTI was obtained from the view with flow most parallel to the insonation beam with a PW sample volume in the center of the annular orifice at the level of the annular plane during diastole. This method assumes a flat velocity profile, but given the annular shape and size and the complex flow pattern of the two cava veins, annular flow is not likely to be uniform, and this calculation may overestimate stroke volume and the actual regurgitant flow. Finally, the reference stroke volume can be selected from the right or left ventricle outflow tract, the mitral inflow, or the left ventricle volumetric stroke volume. These reference parameter have demonstrated reasonable accuracy (standard error ± 10%)[50].

Grading the Severity of Chronic TR by Echocardiography			
TR Severity	Mild	Moderate	Severe
Structural	Bolded signs are considered specific for their TR grade.		
TV morphology	**Normal or mildly abnormal leaflets**	Moderately abnormal leaflets	**Severe valve lesions** (e.g., flail leaflet, severe retraction, large perforation)
RV and RA size	Usually normal	Normal or mild dilation	Usually dilated[1]
Inferior vena cava diameter	Normal <2 cm	Normal or mildly dilated 2.1-2.5 cm	Dilated >2.5 cm
Qualitative Doppler	Bolded signs are considered specific for their TR grade.		
Color flow jet area[2]	**Small, narrow, central**	Moderate central	**Large central jet** or eccentric wall-impinging jet of variable size
Flow convergence zone	**Not visible, transient or small**	Intermediate in size and duration	**Large throughout systole**
CWD jet	**Faint/partial/**parabolic	Dense, parabolic, or triangular	Dense, often triangular
Semiquantitative	Bolded signs are considered specific for their TR grade.		
Color flow jet area (cm^2)[2]	Not defined	Not defined	**>10**
VCW (cm)[2]	<0.3	0.3-0.69	**≥0.7**
PISA radius (cm)[3]	≤0.5	0.6-0.9	**>0.9**
Hepatic vein flow[4]	Systolic dominance	Systolic blunting	**Systolic flow reversal**
Tricuspid inflow[4]	**A-wave dominant**	Variable	E-wave >1.0 m/s
Quantitative			
EROA (cm^2)	<0.20	0.20-0.39[5]	≥0.40
RVol (ml/beat)	<30	30-44[5]	≥45

[1]RV and RA size can be within the "normal" range in patients with acute severe TR.
[2]With Nyquist limit >50-70 cm/s.
[3]With baseline Nyquist limit shift of 28 cm/s.
[4]Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).
[5]There are little data to support further separation of these values.

Figure 18. Summary of the American Society of Echocardiography recommendations for TR grading severity.

3D Echocardiography: this technique has achieved important progress in the last years, but still challenges in volumetric quantification of the right ventricle with possible underestimation of its volumes still remain, especially in case of dilated right chambers. Different studies demonstrated the feasibility and usefulness of 3D color Doppler to quantify the TR, demonstrating an incremental diagnostic value for evaluating the tricuspid valve[51,52]. However a certain variability in cut-off value for severe TR has been reported likely due to the different criteria used to defined severe TR and the lack of a true "gold standard" comparator.

Proposed grading scheme: the traditional grading scheme of TR is divided intop mild, moderate, and severe classes. A VC ≥ 0.7 cm, EROA of ≥ 0.40 cm^2, and regurgitant volume ≥ 45 ml qualify as severe TR with the guidelines advocating a multi-parametric and semiquantitative or quantitative approach[53]. The end-stage patients have late presentations with a degree of TR often referred to as massive; however, this term could fail to capture the severity of the regurgitation and the window of treatability. The Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation (SCOUT) trial demonstrated a reduction in quantitative EROA of −0.22 ± 0.29 mm^2 (the equivalent of a full grade). However the baseline quantitative EROA was 0.85 ± 0.22 mm^2 and the resulting EROA was 0.63 ± 0.29 mm^2. Despite the reduction in TR severity from 'severe TR' to 'severe TR', the SCOUT trial showed that the equivalent quantitative reduction of a 'grade' of TR was associated with an increase in forward stroke volume and resulted in significant improvements in quality of life measures. To better characterize the severity of TR currently being treated with various transcatheter devices, Chan et al.[3] proposed increasing the grades to include very severe (or massive) in addition to torrential.

Parameters	MILD	MODERATE	SEVERE	MASSIVE	TORRENTIAL
Vena Contracta width (biplane average)	<3 mm	3-6.9 mm	7 mm - 13 mm	14-20 mm	≥21 mm
EROA by PISA	<20 mm^2	20-39 mm^2	40-59 mm^2	60-79 mm^2	≥80 mm^2
3D Vena Contracta Area or Quantitative Doppler EROA	-	-	75-94 mm^2	95-114 mm^2	≥115 mm^2

Example:

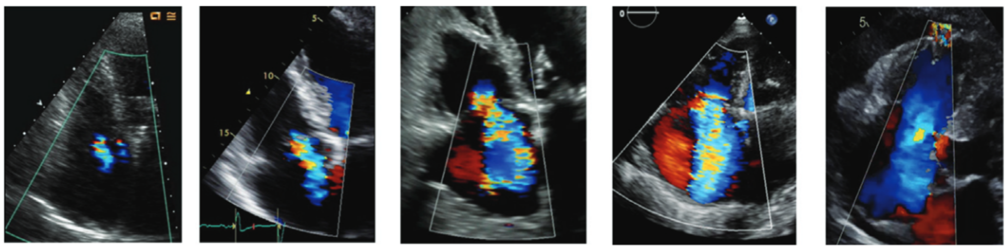

Figure 19. A new grading scheme, which extends the severity scale for TR to "massive" and "torrential", has recently been proposed. Because of the crescent shape of the TR orifice, the VC width is the average of 2 orthogonal views. The proximal isovelocity surface area (PISA) method for calculating EROA may be smaller than the EROA obtained by either 3D planimetry of the VC area or by quantitative Doppler calculations.

CMR

Magnetic resonance imaging (MRI) technology applies a strong magnetic field to align the body's protons (namely, hydrogen ions) after which radio waves are then generated to disrupt proton alignment. As the protons realign themselves to the magnetic field, they emit radio signals that the computer device reads and converts into detailed spatiotemporal images[54]. High-resolution, multiplanar images obtained using cine-MRI provide doctors with comprehensive information about the morphology and function of the scanned structure. Thus, cardiac magnetic resonance (CMR) assessment of TR is feasible but less established than that of other regurgitant valvular lesions. Evaluation of associated right-sided chamber remodeling and function is an important feature of CMR, which does not require use of contrast. Direct and indirect methods to quantify the TR have been proposed, but the validation is not optimal yet because the lack of adequate reference standards.
Qualitative assessment: CMR is capable of providing a view of the right sided chamber size and function without the use of ionizing radiation and contrast agents. The TV anatomy can be studied in multiple planes, which requires appropriate planning and slice selection (Figure 20).

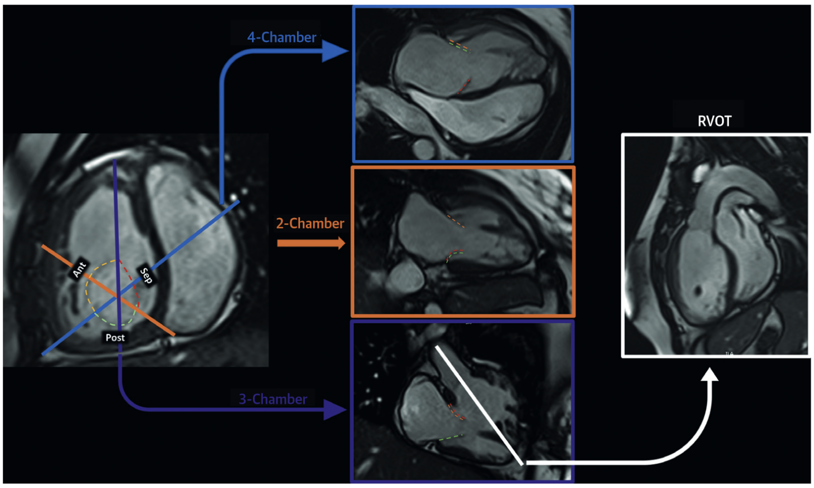

Figure 20. Cardiac magnetic resonance (CMR) prescription planes used for evaluation of the right ventricle (RV) and tricuspid valve (TV)

Qualitative evaluation of TR by CMR is obtained by visualising the area of local signal drop that occurs due to the flow turbulence and/or acceleration. However the visual qualitative approach has demonstrated moderate correlation with the quantitative method and important caveats exist, including the appearance of the regurgitant jet is affected by plane, slice thickness, windowing, and echo time[55]; therefore, fine degrees of TR differentiation are often challenging.
Quantitative assessment: CMR has usually been considered the gold standard technique for quantitative valvular assessment. However, CMR-specific cutoff values for TR severity derived from regurgitant volume *and* regurgitant fraction are currently unknown. The latest guidelines suggest adopting the same regurgitant fraction severity thresholds for TR that have been used for MR (namely, a regurgitant fraction of ≤15% for mild TR, 16% to 25% for moderate TR, 26% to 48% for moderately severe, and >48% for severe TR[53]).
Indirect calculation of regurgitant volume: CMRI is considered the "gold standard" for reliably and accurately measuring the ventricular volumes, ejection fraction, and the myocardial mass[56] due to the complex shape of the RV in addition to the excellent endocardial definition. Volumetric analysis of the RV is acquired without geometric assumption by measurement of a short axis stack of cine-CMR images from the base to the apex. After calculation of the RV volumetric stroke volume (RVSV), the tricuspid regurgitant volume (RVol) is then derived as total RVSV minus a reference systemic SV. Three possible reference SVs, which can be subtracted to obtain the RVol, can be used: (1) phase-contrast (PC) imaging of the pulmonic valve in the absence of pulmonic regurgitation (2) PC imaging of the aortic valve in the absence of aortic regurgitation, and (3) volumetric LVSV in the absence of aortic or mitral regurgitation. If possible, RVol should be obtained using multiple methods to check for internal consistency and increase certainty for the TR severity asssessment.
Direct calculation of regurgitant volume: PC imaging can also be used to directly measure the regurgitant volume. This method has been validated *in vivo* and by invasive flow measurements[57]. Direct PC assessment is challenging because of the significant motion of the non-planar annulus; however, reports of success with this approach are available although this technique has not been widely reported in published studies.
4D flow imaging: a very promising technique is the 4D flow velocity-encoded imaging. This method allows for free breathing and time-resolved whole-heart acquisition with velocity encoding in all directions. 4D flow has been investigated and implemented mostly for the left heart and more validation for TR is needed. Retrospective valve tracking are characteristics available in new 4D flow software and this could be a solution to the issue of in-plane motion of the tricuspid annulus. A recent article reported an excellent correlation of direct measurements of TR using 4D flow with conventional CMR methods[58]. Further clinical and prognostic validation of 4D flow are needed.

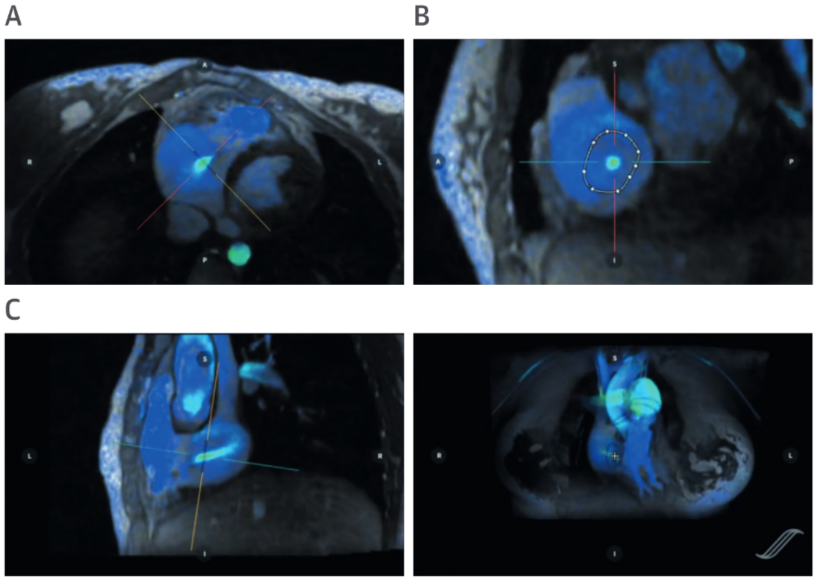

Figure 21. A multiplanar reconstruction still frame from a four-dimensional cardiac magnetic resonane (4D CMR) velocity-encoded acquisition is shown with retrospective valve tracking. In this systolic frame, high-velocity TR flow is represented as a bright green color. The crosshairs can be manipulated in the long-axis images (A and C) to align flow, which can then be measured in the short-axis through-plane of the TR jet (B). Valve tracking (B, polygon) allows semiautomated adjustment of through-plane motion for more accurate assessment of flow.

While MRI produces high-resolution images, the modality is restrictive in practical applications. MRI capabilities are limited in terms of evaluating cases of severe TR due to its inability to be performed on hemodynamically unstable patients. Moreover, patients with permanent pacemakers, implantable cardiac defibrillators, and/or metal prosthetic heart valves cannot undergo an MRI scan unless they have a newer MRI-compatible system.

Cardiac CT

Quantitation of TR has not been systematically investigated using computed tomography angiography (CTA). However, due to the methodological limitations observed with the use of echocardiography (particularly the underestimation of TR severity based on the PISA method and inter-observer variability of the quantitative Doppler method), CTA can provide valuable information in patients with suboptimal transthoracic echocardiographic imaging quality in cases in which unclear TR grading and/or adequate visualization of the right ventricular remodeling and function exists. Furthermore, an integrative approach considering data from several imaging modalities is likely to improve diagnostic accuracy.[59]

CTA scans use X-ray measurements to create 2D radiographic cross-sections of the heart taken around an axis of rotation. Digital processing yields multiplanar 3D reconstructions of the area of interest with desirable spatial and temporal resolution. Thin image slices allow for detection of distinct valvular boundaries and useful spatial information for assessing RV function[60]. Studies support the prognostic value of cardiac CTA for indexing FTR. Such parameters include the RA and RV volumes, the leaflet tethering angles and height, and the annular diameter and area[61,62]. CTA has also been used in the post-operative assessment of annuloplasty ring dislodgment and quantification of the spatial relationship between pacemaker leading in the RV and the associated TR[63]. Despite its attractive capabilities and applications to the heart valve leaflets, CTA exposure must be monitored and limited due to the potential adverse effects of the radiation during the X-ray measurements.

Functional tricuspid regurgitation after mitral valve surgery

The treatment of FTR combined with MV disease has been debate for decades. Based on the seminal paper of Braunwald in 1967[3], it was thought that secondary TR decreases or even disappears after surgical correction of MV disease. This concept was further also supported by the group of Duran et al.[3] in 1980, where they demonstrated a disappearance of FTR after correction of mitral valve disease and reduction of PH therefore demonstrating that the immediate reduction in the afterload of the RV could solve most FTR (Figure 22). Therefore for decades, the TV was neglected and named the forgotten valve.

	Organic disease (n = 14)		*Functional disease (n = 17)*	
	TI present	*TI absent*	*TI present*	*TI absent*
TPR < 500 dynes n = 18)	10 (100%)	0	0	8 (100%)
TPR > 500 dynes (n = 13)	4 (100%)	0	9 (100%)	0

Legend: TI, Tricuspid insufficiency. TPR, Total pulmonary resistances (dynes · sec · cm^{-5}).

Figure 22. Residual TI related to post-operative total pulmonary resistance in 31 patients with no tricuspid repair.

However, already in 1974, Carpentier and colleagues[64] stated a conservative approach to concomitant tricuspid repair could be "dangerous," but it took another decade for the impact of severe heart failure due to TR years after isolated mitral surgery and the high mortality associated with reoperative tricuspid surgery to be widely recognized[65]. King et al. describe reintervention in 32 patients who developed FTR after MV surgery. In this report, they documented a hospital mortality of 25%, and all early deaths were related to low cardiac output. Among hospital survivors there have been 14 late deaths for 3- and 5-year actuarial survival rates of 65% and 44%, respectively. Therefore, they concluded that re-operative TV surgery carries a high early and later mortality risk related to RV failure and dilatation and that restoring TV competence could be seen as palliative.

The beginning of the debate

In 2005, Dreyfus et al.[3] introduced the concept of treating the TV in function not only in terms of TR degree but also in terms of function of the annulus dilatation. Both annulus and RV dilatation would precede the appearance of TR. We know that FTR occurs and may vary in function of preload, afterload and function of the right ventricle. Therefore, the FTR can change considerably in degree and severity after modifications of one or more of these factors, which is why only the severity of FTR is debated as an adequate indicator for treatment. Using this concept the authors treat, during a period of 12 years, 311 patients with chronic severe mitral regurgitation. During this procedure, the surgeon measured the TA directly after cardioplegic arrest of the heart. The patients were divided into two groups according the presence of annular enlargement, which was defined as > 70mm, corresponding a two-fold diameter of the normal value (Figure 23). Group 1 had no dilatation and underwent isolated mitral valve repair ([MVR]=163 patients), and Group 2 with dilatation underwent MVR and tricuspid annuloplasty (n=148 patients).

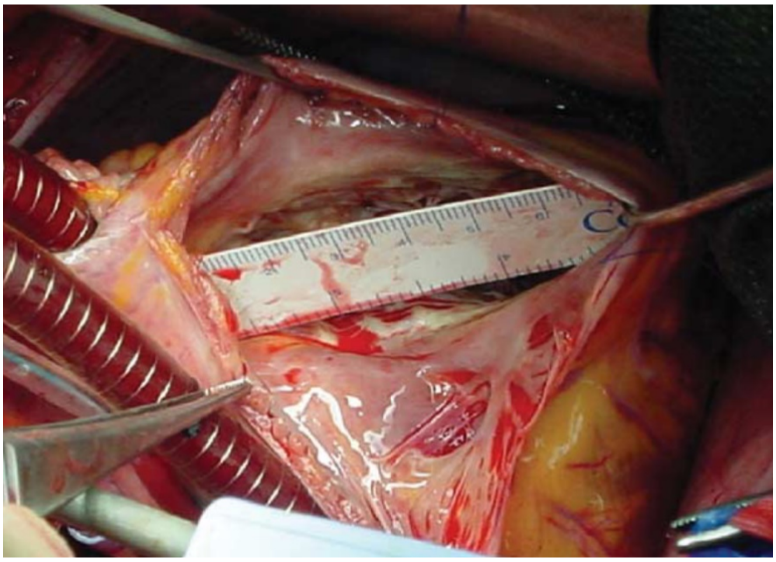

Figure 23. Measurement of the tricuspid annular diameter from the anteroseptal commissure to the anteroposterior commissure using a sterile supple ruler.

At a 4.8-year follow-up, a significant reduction in FTR and an improved New York Heart Association (NYHA) class with a same rate of mortality and morbidity (pace-maker, stroke, myocardial infarction) were demonstrated. They further proved that the FTR is an ongoing process since during the follow - up, an increase in TR by at least two degrees in 45% of the patients who received isolated MVR. Eleven patients graded 0 pre-operatively were assessed as grade IV at follow-up, and 38 patients graded I pre-operatively were assessed as grade III at follow-up and this with a residual pulmonary pressure were not substantially different in both groups. They finally concluded that contrary to current beliefs, TR does not spontaneously disappear once the left lesion has been corrected and that the data demonstrate that once the annulus is dilated and consequently, the RV function becomes mildly impaired, the process of TR is progressive and will subsequently become clinically relevant.

Advantages

This paper was further used by a different author to support this more aggressive approach for treating the TV.

The first report supporting this hypothesis was the paper of Van De Veire et al.[66]. The authors studied two separated cohorts of patients treated in different chronological periods, one in 2002 and the second in 2004. In the 2002 cohort, TA was performed only when the pre-operative echocardiography demonstrated a TR of grade 3 or 4. In the 2004 cohort, tricuspid valve annuloplasty (TVA) was performed when the pre-operative echocardiography demonstrated a TR of grade 3 or 4 or in any case when TA enlargement (> 40 mm) had been observed. This threshold was introduced for the first time and derived in a paper of Sugimoto et al.[67] who identified a TA diameter of 40 mm as predictor of right heart failure in patients undergoing left heart surgery.

In the cohort of 2002, in patients with TR, the regurgitation improved, and the RV dimension decreased. The patients without pre-operative TR of grade 3 or 4 but with a dilated annulus had a higher degree of TR at the 2-year follow-up and a more dilated RV in terms of basal and long diameter, while the patients without TA dilatation demonstrated stable TR and RV dimension (Figure 24).

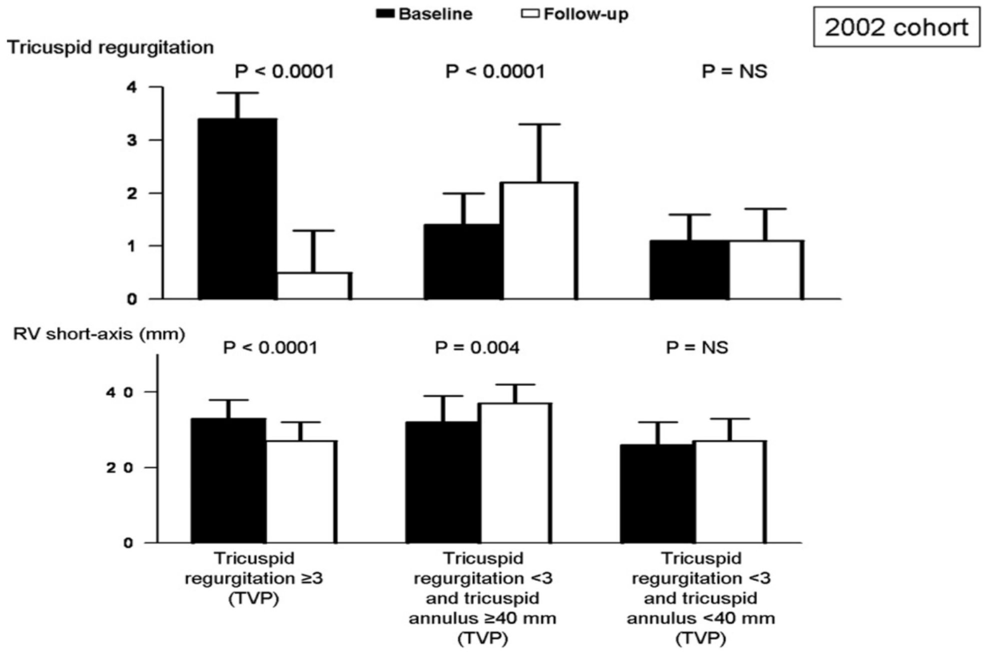

Figure 24. echocardiography evaluation of TR and RV basal dimension at baseline and at the 2-year follow-up in the 2002 cohort according to subgroups.

The cohort of 2004 in which patients underwent annuloplasty in cases of TR degree of 3 or 4 or TA dilatation. Both groups of patients with severe TR or dilatation had a significant decrease in TR at 2 years follow-up, and they showed a decrease in RV dimension indicating reverse RV remodeling (Figure 25).

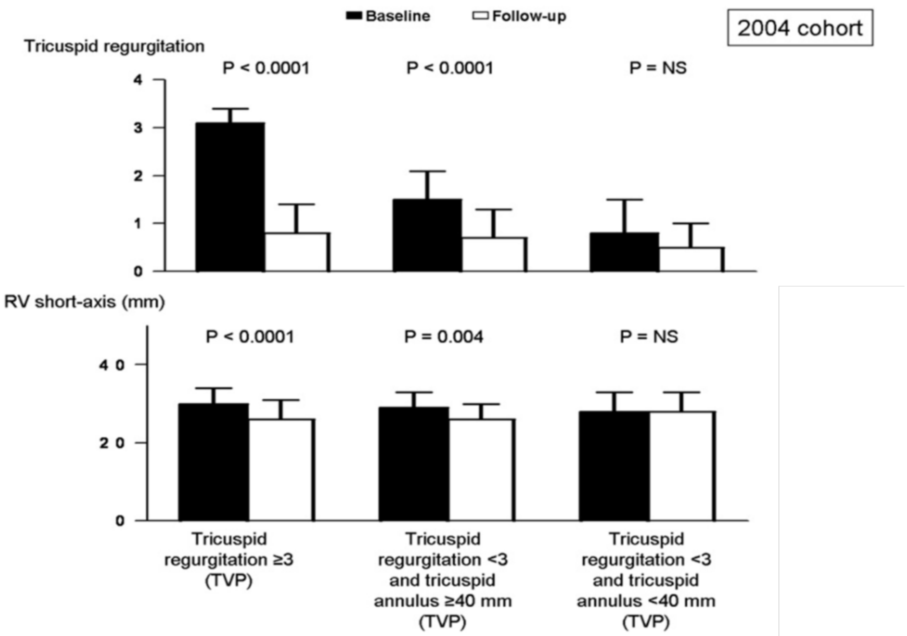

Figure 25. echocardiography evaluation of TR and RV dimension at baseline and the 2-year follow-up in the 2004 cohort according to subgroups.

Based on these findings, the authors then concluded that combined MVR and TA should be considered in patients with annular dilatation despite the absence of TR at baseline.

Another article supporting this thinking was published in 2015 by Chickwe at al.[68]. In this study involving 645 consecutive patients undergoing repair of degenerative mitral regurgitation between 2003 and 2011, 419 (65%) underwent concomitant TA. Several indications for TVR were present: i. moderate or greater TR; ii. significant annular dilatation assessed on the pre-bypass echocardiography at end-diastolic diameter on the 4-chamber view as an annulus > 40 mm; or iii. in case of equivocal findings , on the basis of direct assessment, intra-operative saline testing, and/or comparison of the anterior and posterior leaflet surface area with the annulus size. This strategy almost eliminates residual and recurrent TR without incremental risk. Importantly, using this strategy allowed TVR to achieve superior freedom from TR in addition to improved RV function and PH in patients with worse baseline risk factors when compared with MV repair only (Figure 26).

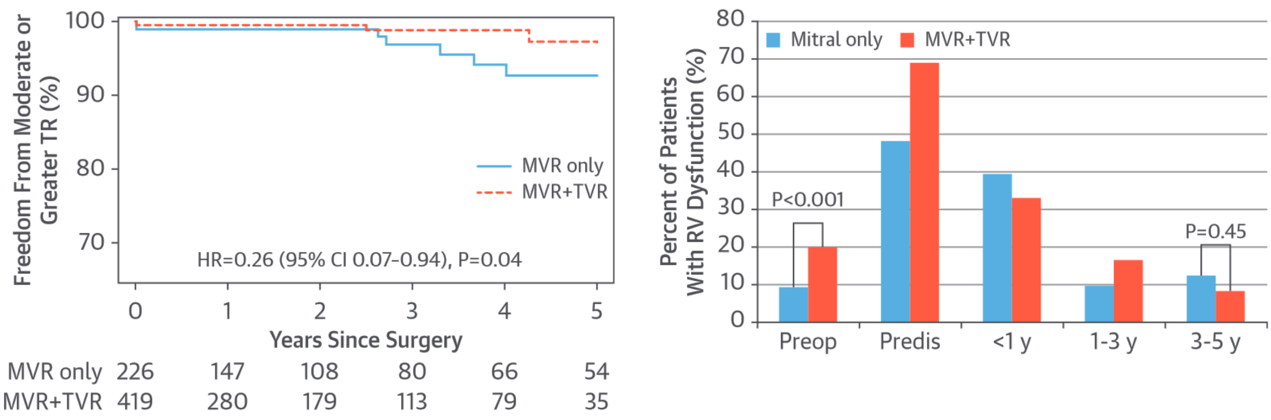

Figure 26. Left panel: freedom from late moderate TR; Greater freedom from late moderate TR was observed in patients who underwent MVR and TVA (red dotted line) when compared with those who underwent only MVR (blue solid line). Right panel: Longitudinal change in proportion of patients with RV dysfunction.

Drawbacks

The presentation of the previous study at the 2015 Annual Meeting of the American Association for Thoracic Surgery prompted the study of David et al.[3] who argued that the rate of TVA was excessively high and unnecessary. In their study, they examined the incidence of TR and its consequence in a large cohort of patients who underwent MVR due to degenerative disease over the last three decades. In more than 1100 patients, TR was infrequently addressed during the first half of this experience, and only patients with evidence of right-side failure had undergone TVA. Over time, moderate or severe TR at the time of MVR that was performed for degenerative diseases of the MV was associated with impaired LV function, atrial fibrillation (AF), and more advanced symptoms of congestive heart failure. They stated that most likely these patients should have undergone TVA. In the whole series, the rate of TVR was 4.7%. Even with such a conservative policy, the rate of TR reached an estimated risk of moderate or severe TR of 13.6% at the 15-year follow-up, and they also found that unrepaired moderate or severe TR was one of the major predictors of FTR at follow-up (Figure 27). Therefore they concluded that TR after MVR is uncommon, and only the patients with moderate and severe pre-operative TR should be treated with annuloplasty.

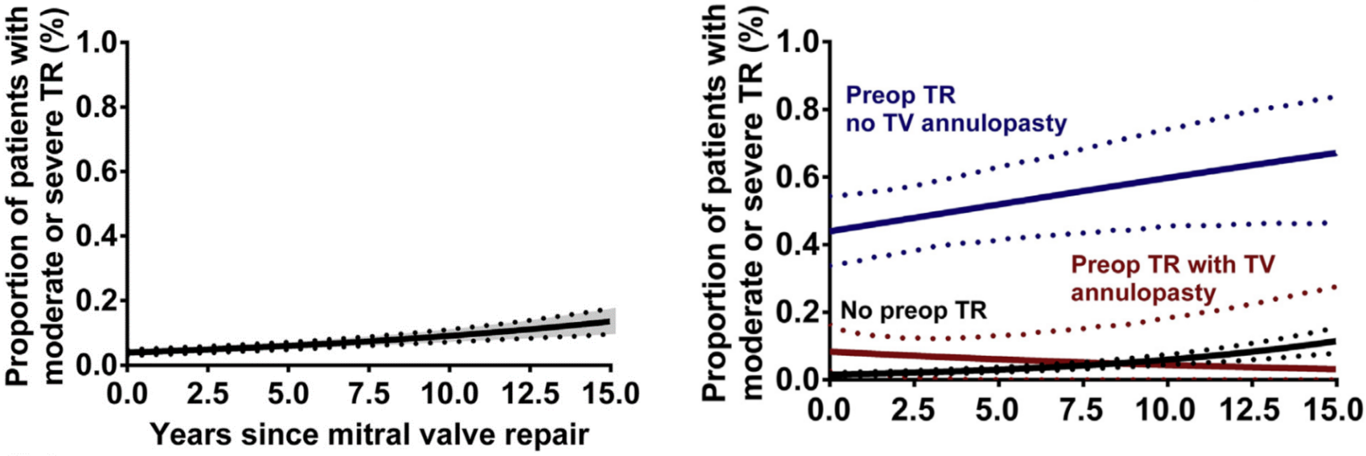

Figure 27. Incidence of moderate/severe TR over time for all patients (left panel) and stratified by preoperative tricuspid valve regurgitation and concomitant tricuspid annuloplasty (right panel).

In a second manuscript by David et al.[69], the tricuspid annulus was measured in 312 consecutive patients in case of isolated MVR to test if this measure was predictive or correlated to development of FTR. The mean annulus diameter was 36 mm and was dilated (≥ 40 mm) in 80 patients. At a follow-up of 6.7 years, moderate or severe TR was 6.6% for all patients, 6.8% for TA < 40 mm, and 6.0% for TA ≥ 40 mm. Pre-operative annulus diameter was not associated with the risk of developing post-operative TR based on either univariable or multivariable regression models. In these analyses, pre-operative TR was the strongest predictor of post-operative TR.

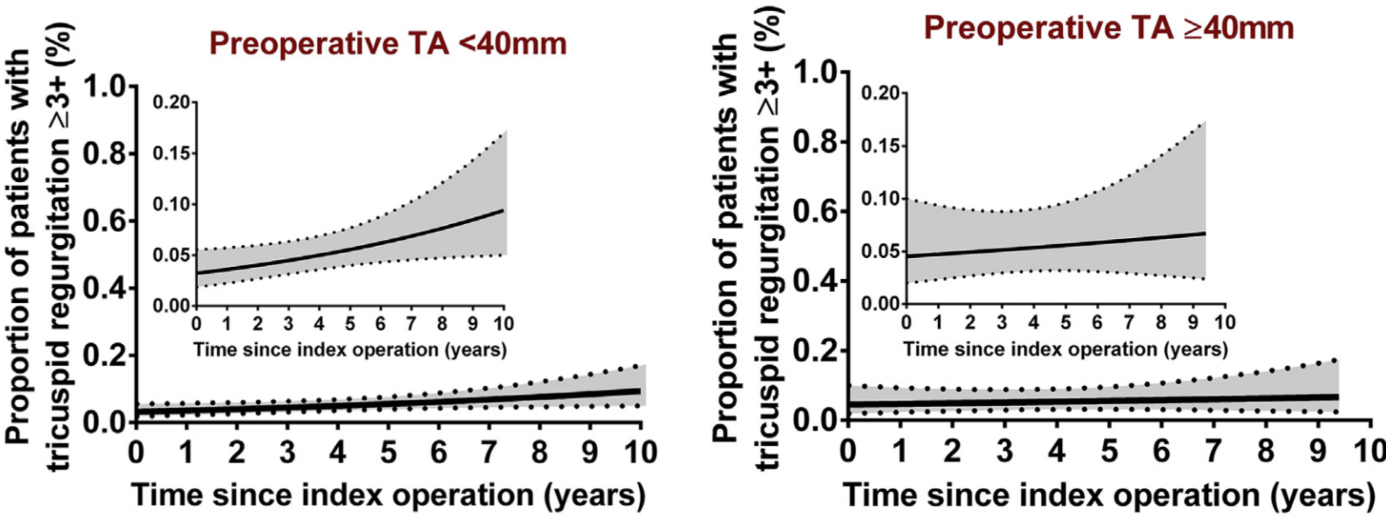

Figure 28. Estimated punctual probability of post-operative TR of moderate degree or increasing over time.

A possible explanation proposed by David was that the cut off of 40 mm could not be applied to the global population of degenerative mitral disease because the TV leaflets vary in size. Patients with fibroelastic deficiency frequently have small TV leaflets for which a TA of 40 mm is likely too large. This TVA is probably necessary to prevent late TR. On the other hand, patients with myxomatous degeneration of the MV frequently have large leaflets with a large mitral annulus and also large TV leaflets with larger TAs. This type of degenerative disease is present in most of these patients, and a TA of 40 mm is likely normal and is only rarely associated with severe TR.

Another paper challenges the concept that TA > 40 mm is predictive of post-operative FTR after MV repair for degenerative diseases. Sordelli and colleagues[3] prospectively evaluated the predictive value of TA diameter assessed by 3D transesophageal echocardiography in the development of TR in 706 patients who had undergone isolated MVR for MR due to degenerative diseases (77% with myxomatous diseases with a broad spectrum of lesions and 23% with fibroelastic deficiency). They completed a detailed analysis of the diastolic and systolic TA diameters (anteroposterior and septolateral) and the outcomes of surgery after a mean follow-up of two years. TR diminished by one grade in 32% of the patients, remained unchanged in 62%, and increased by one grade in 5.5%, but only three patients developed moderate or severe TR. The authors concluded that "newly developed significant TR is a rare event after successful repair of degenerative MR" and that "analysis of TA does not predict early to midterm subsequent TR progression." Based on a multivariate regression analysis, recurrent MR and PH at follow-up emerged as significant positive predictors of TR progression.

An article from the Cleveland clinic[70] support the less aggressive approach proposed by David. Treating only patients with moderate TR or greater in cases of left-heart sided disease and rather not with annular dilatation, they obtained a rate of FTR of 7% in the group treated with an annuloplasty and 15% in the untreated group. Major risk factor for TR at follow up was the grade ¾ TR for the procedure and not annular dilatation. Later in an editorial in response to the paper of David, Gillinov et al.[3] confirmed the concept of treating the TV during MV surgery mainly when TR is moderate, but they also considered adequate the use of annuloplasty in cases of annular dilatation and mild TR. They pointed out also that the management of TR is based on a retrospective clinical series; therefore, it is necessary to conduct a randomized controlled trial to settle this controversy.

What the guidelines say

After the seminal paper of Dreyfus, the ESC guidelines introduced for the first time the concept of treating the TV irrespective of the TR degree but in the presence of annulus dilatation, sign already the definition of < 40mm[71]. Subsequently, also the American College of Cardiology and American Heart Association guidelines state that TVA might be considered in patients undergoing MV surgery when tricuspid annular dilatation is present, but they did not specify the threshold. Since then, the guidelines published from both American and European societies have remained unchanged (Table 4).

ESC/EACTS 2012		
Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation (TR) with a dilated annulus (>_40 mm or > 21 mm/m² by two-dimensional echocardiography) undergoing left-sided valve surgery.	IIa	C
ESC/EACTS 2017		
Surgery should be considered in patients with mild or moderate secondary TR with dilated annulus (≥ 40 mm or > 21 mm/m²) undergoing left-sided valve surgery.	IIa	C
ACC/AHA 2020		
In patients with progressive TR (Stage B) undergoing left-sided valve surgery, tricuspid valve surgery can be beneficial in the context of either i. tricuspid annular dilation (tricuspid annulus end diastolic diameter > 4.0 cm) or ii. prior signs and symptoms of right-sided heart failure.	IIa	B-NR
ESC/EACTS 2021		
Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus (≥ 40 mm or > 21 mm/m² based on 2D echocardiography) undergoing left-sided valve surgery	IIa	B

Table 4. Chronological guidelines indication for tricuspid regurgitation (TR) in cases of dilatation of the annulus.

ESC: European Society of Cardiology; EACTS: European Association for Cardio-Thoracic Surgery; ACC: American Collef of Cardiology; AHA: American Heart Association

Also, the most recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines state that surgery should be considered in patients with mild or moderate FTR and dilated annulus (> 40 mm or > 21 mm/m^2) undergoing left-sided valve surgery.

As already stated, different authors highlight that this specific recommendation has a class of Recommendation IIa and a level of evidence B, indicating that the data were derived from a single randomized clinical trial or large non-randomized studies. Therefore, the need from data originating from a randomized controlled clinical trial to confirm this indication and increase the level of evidence is present.

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Aims of the thesis

As outlined in the previous chapter, the actual data used by the current guidelines for the treatment of FTR at the time of left-side heart valve disease are based on a retrospective single center series. Over the last 15 years, the debate to be or not be more aggressive in terms of treating the TV has not progressed much.

The aims of the present thesis are to elucidate different aspects of this debate.

The first aim will investigate the role of TVA at the time of MV surgery in cases of less than severe TR irrespective of annular dimension. To test this hypothesis, we designed a single center prospective randomized controlled trial that included patients undergoing MV surgery and randomizing them to receive or not receive a TVA to evaluate whether annuloplasty prevents TR progression after MV surgery and whether this procedure is associated with improved RV re-modeling or provides a functional benefit.

In the second aim of this work, we question whether the TA diameter is the correct parameter to describe annular dilatation. The TV has a irregular non circular shape. This shape even becomes exaggerated in the presence of FTR as the anterior and posterior parts of the annulus tend to dilate more than the septal part. This process makes it difficult to accurately measure tricuspid annular dimensions from a single 2D-echo cross section. 3D echocardiography has been shown to overcome the limitations of 2D echo in non-circular objects. To test the difference betweenthe two measurements, we compared 2D and 3D measurements of the TA with their intra-operative equivalents to understand the most adequate parameter to describe the TV anatomy. We also compared 3D measurements of valve leaflet areas and lengths with those obtained during surgery.

Finally, the last goal of this work was to study additional actual and novel 3D echocardiographic parameters to identify patients who will develop or exhibit persistent moderate or severe FTR. To test this hypothesis, we selected patients from the initial randomized study who had not undergone TVA. Using these post-operative 3D echocardiographic images, we examined several new parameters to identify the predictors of persistence or regression of FTR at follow-up.

Midterm results of a randomized trial of tricuspid annuloplasty for less than severe functional tricuspid regurgitation at the time of mitral valve surgery.

Midterm results of a randomized trial of tricuspid annuloplasty for less than severe functional tricuspid regurgitation at the time of mitral valve surgery.

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Abstract

Objectives: The optimal management of functional tricuspid regurgitation (FTR) in the setting of mitral valve (MV) operations remains controversial. The current practice is both center- and surgeon-specific with guidelines based on non-randomized data. A prospective randomized trial was performed to evaluate the worth of less-than-severe FTR repair during mitral valve procedures.

Methods: A single center randomized study was designed to allocate patients with less-than-severe FTR undergoing MV surgery to be prophylactically treated with tricuspid valve annuloplasty (TVP^- or TVP^+). These patients were analysed using longitudinal cardiopulmonary exercise capacity, echocardiographic follow-up, and cardiac magnetic resonance (CMR). The primary outcome was freedom from more or equal than moderate tricuspid regurgitation (TR) with vena contracta (VC) ≥ 4 mm. Secondary outcomes were maximal oxygen uptake (VO_2 max) and right ventricular (RV) dimension and function.

Results: A total of 53 patients were allocated to receive a concomitant TVP^+, and 53 patients were treated conservatively (TVP^-). At five years, TR > mild was observed in 10 (TVP^-) and no patient (TVP^+; $p < 0.01$). VO_2 max, RV basal diameter, end-diastolic and -systolic diameter, and fractional area changes were similar in both groups. CMR confirmed no differences in RV end-diastolic, end-systolic volume, and RV ejection fraction.

Conclusion: This single-center prospective randomized trial demonstrated that prophylactic tricuspid annuloplasty irrespective of annular dilatation at the time of mitral surgery led to a reduction in the recurrence of moderate or severe FTR at the 5-year follow-up and a reduction in pulmonary pressure. Nevertheless, the functional capacity, RV function, and dimension remained similar.

Introduction

Functional tricuspid regurgitation (FTR) during left-sided surgery has been treated only when severe and surgical tricuspid repair had been avoided for years because of the concept that tricuspid regurgitation (TR) should disappear once the primary left-sided problem was eliminated [1]. However, moderate to severe late FTR has been reported in up to one-third of the patients after isolated mitral valve (MV) surgery for rheumatic [2], functional, ischemic [3], and degenerative MV disease [4]. Severe FTR late after cardiac surgery is associated with substantial morbidity and mortality [5] and is also done in order to avoid high risk reoperations. Dreyfus proposed that annular dilatation should be considered as much as, if not more than, FTR grading. Tricuspid regurgitation (TR) is a less reliable parameter because it depends on many factors, including preload, afterload, and right ventricular (RV) function. Treating annular dilatation beyond a given size has been shown to improve functional status with a trend toward better survival when compared with a group of patients who did not receive tricuspid annuloplasty (TA), irrespective of TR severity [4]. Many publications reinforce this concept [6–8], and European and American association guidelines include the annular size of the tricuspid valve (TV) with a threshold diameter of 40 mm as a type IIa recommendation [9, 10]. The aforementioned threshold of 40 mm is derived from a published retrospective study that compared two patient cohorts treated during different historical periods [7] and found a higher rate of TR in patients with dilated annulus (≥ 40 mm).

Only one small prospective randomized study has been published reporting one year clinical and echocardiographic results [11] in patients with less-than-severe TR and annular dilatation.

We designed a prospective single-center randomized study to test the hypothesis that concomitant TA in patients treated for left-heart valve disease prevents an improvement in TR progression after MV surgery and to evaluate whether this process is associated with an improvement in right ventricular (RV) re-modeling or a functional benefit irrespective of the annular dimension.

Methods

Among 139 consecutive patients undergoing MV surgery (either repair or replacement) between May 2009 and December 2010, 106 patients with less-than-severe functional TR (< 7mm vena contracta [VC])[12] were enrolled. Exclusion criteria consisted of several parameters: (1) presence of pacemaker leads through the tricuspid valve, (2) acute endocarditis, (3) minimally invasive approach, and/or (4) type IIIb mitral valve insufficiency. Tricuspid annular dilatation (>40 mm or >21mm/m2) was not considered an inclusion criterion.

A total of 53 patients were allocated to receive a concomitant tricuspid valve annuloplasty (TVP^+) compared to 53 patients treated conservatively (TVP^-) at the time of MV surgery. Participants in each group were analysed according to the "intention-to-treat" principle. The local ethics committee approved this study, and each patient signed an informed consent form.

<u>Clinical and functional assessments</u>

At baseline and during each year of follow-up, the functional New York Heart Association (NYHA) class was assessed. A cardiopulmonary exercise test was performed in 61 and 60 patients at one and three years, respectively). Symptom-limited treadmill exercise testing with respiratory gas exchange analysis used a modified Bruce protocol (2-min workloads, 2 W/min increments in work). Electrocardiographs were continuously monitored, and blood pressure was assessed during the last 30 s of each 2-min workload. Patients were encouraged to exercise to exhaustion. Oxygen consumption (VO_2) was measured using a Medical Graphics metabolic cart, and peak VO_2 was taken as the highest average 30-sec VO_2 during exercise and expressed as absolute peak VO_2.

Echocardiography

A transthoracic echocardiography was obtained within seven days before the surgery and then yearly in our valve clinic; the last available echocardiographic analysis was used as follow up. Technicians performed the transthoracic echocardiography, and an experienced and dedicated cardiologist with a specific sub-specialisation in cardiac imaging validated the images. echocardiography data were obtained with commercially available ultrasound systems. All patients had a comprehensive examination, including M-mode and 2-dimensional (2D) echocardiography in addition to conventional and color Doppler examinations. All tests were conducted by experienced technicians. Carpentier classification was used to describe MV disease. The proximal isovelocity surface area (PISA) method with evaluation of effective regurgitant orifice and regurgitant volume were used to quantify mitral valve regurgitation (MVR) [13]. FTR grading was based on the VC width measured from an apical 4-chamber view and defined based on three categories: (1) mild < 3 mm; (2) moderate between 3 and 6 mm; or (3) severe ≥ 7 mm [12].

Right and left chambers (atrial and ventricular) dimensions and systolic pulmonary artery pressures (using TR velocity) and functions were measured as recommended by Lang [14].

Cardiac Magnetic Resonance

At six months post-surgery, 30 patients (18 in TVP^- versus 12 in TVP^+) underwent a cardiac magnetic resonance (CMR) study. A standardized CMR protocol was performed using a 1.5-T Intera CV scanner (Philips Medical Systems, Best, The Netherlands) as described previously [15]. Briefly, 10–12 consecutive short-axis cine steady-state free precession images covering the entire LV and RV areas were acquired for myocardial function assessment. Ten to 15 min after injection of gadolinium-based contrast, identical prescriptions of short- and long-axis slices were acquired for myocardial viability assessment. CMR images were analyzed using Segment 1.9 software (http://segment.heiberg.se). LV and RV volumes and ejection fractions (EFs) were obtained by manual tracing of contours on the short-axis images in end-diastole and end-systole. A dedicated cardiologist evaluated and performed the measurement.

Surgical procedure

All operations were performed through a median sternotomy using standard aortic and bicaval venous cannulation. The patients were fully heparinized and placed on normothermic cardiopulmonary bypass (CPB). The MV was exposed through a left atriotomy. Whenever possible, MV repair was performed following the classical Carpentier approach. In all repair cases, a semi-rigid annuloplasty ring was used to complete the procedure. In case of MV replacement, the posterior leaflet was preserved, and 2-0 polyester valve sutures were used. If chordal preservation was not feasible, artificial polytetrafluoroethylene chordae were implanted from the papillary muscles (PM) to the posterior sewing ring.

Tricuspid annuloplasty (TA) was performed using a semi rigid ring (Carpentier–Edwards rings were used most of the time and just three Medtronic contour 3D ring). The size was chosen based on the function of the area of the anterior leaflet of the TV. This area should match the tricuspid ring sizer.

Outcomes

The primary outcome was freedom from more or equal than moderate TR (VC ≥ 4mm), freedom from severe TR (VC ≥ 7mm), and progression of FTR defined as an increase of > 3 mm VC between pre-operative and follow-up echocardiographyexaminations. Secondary outcomes included VO_2 max, RV dimension and function, freedom from TV reoperation, cardiac-related death, and New York Heart Association (NYHA) class > II.

Statistical analysis

All analyses were conducted using the RStudio software (Version 1.0.153–© 2009–2017 RStudio, Inc.). Continuous variables were expressed as mean ± standard deviation (SD), categorical variables were expressed as counts and percentages, and follow-up times as median and range. Patients' characteristics were compared between two groups with Student's t- or Mann-Whitney U test for continuous variables or chi-squared or Fisher's exact test for dichotomous variables where appropriate. A probability value of 0.05 was considered indicative of a statistically significant difference.

A Kaplan–Meier analysis was used to analyze the the freedom from TR, MR, MV reoperation, and NYHA > II [16]. A log-rank test was used to compare the two groups.

Cox proportional hazards regression model was used to evaluate the possible association between the freedom from moderate or more TR based on the clinical and echocardiographic parameters. A sample size of 49 patients per group was calculated using the reference incidence of recurrence of FTR at 5 years of 25%, a type I error of 5%, a type II error of 20%, and risk ratio of 0.2 [17].

Results

Pre-operative Characteristics

Pre-operative patient demographics are listed in Table 1. No statistically significant differences between the two groups with regard to age, sex, history of atrial fibrillation, previous myocardial infarction, NYHA functional class, and VO_2 max were found. The underlying valvular lesion of the MV was similar in both groups with the predominant lesion being a degenerative mitral valve regurgitation (MVR). Mitral stenosis was similar in 11 TVP^- patients and 10 TVP^+ patients (p = 0.9).

Echocardiographic characteristics are presented in Table 2. Left ventricular (LV) dimensions, volumes, and function were comparable between the two cohorts. TR grade was similar between both cohorts as were RV dimensions and function.

Table 1: Preoperative characteristics

	TVP- (*N* = 53)	TVP+ (*N* = 53)	*P*-value
Age (years), mean ± SD	62.1 ± 14.5	64.2 ± 13.7	0.44
Male gender, *n* (%)	33 (62.3)	36 (67.9)	0.68
Hypertension, *n* (%)	22 (41.5)	23 (43.4)	1.00
Diabetes, *n* (%)	3 (5.7)	5 (9.4)	0.72
Smoker, *n* (%)	10 (18.9)	8 (15.1)	0.80
COPD, *n* (%)	5 (9.4)	2 (3.8)	0.44
Renal failure, *n* (%)	3 (5.7)	1 (1.9)	0.62
PVD, *n* (%)	3 (5.7)	1 (1.9)	0.62
CVA, *n* (%)	1 (1.9)	5 (9.4)	0.21
Beta-blockers, *n* (%)	22 (41.5)	26 (49.1)	0.56
ACE inihibitor, *n* (%)	17 (32.1)	17 (32.1)	1.00
Diuretics, *n* (%)	13 (24.5)	14 (26.4)	1.00
Redo, *n* (%)	3 (5.7)	2 (3.8)	1.00
NYHA class, mean ± SD	2.1 ± 0.8	2.2 ± 0.9	0.65
Weight (kg), mean ± SD	71.6 ± 15.4	75.1 ± 16.0	0.26
Length (cm), mean ± SD	169.3 ± 9.8	170.0 ± 11.5	0.74
AF persistent, *n* (%)	6 (11.3%)	7 (13.2%)	1.00
AF permanent, *n* (%)	5 (9.4%)	10 (18.9%)	0.26
MV pathology, *n* (%)			
Degenerative	33 (62.3)	31 (58.5)	0.84
Barlow	7 (13.2)	9 (17.0)	0.79
Rheumatic	13 (24.5)	13 (24.5)	1.00

ACE: angiotensin converting enzyme; AF: atrial fibrillation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; MV: mitral valve; NYHA: New York Heart Association; PVD: peripheral vascular disease; SD: standard deviation; TVP: tricuspid valve annuloplasty.

Table 2: Echocardiographic data (preoperative vs follow-up) of the atria and left ventricle

	TVP-, mean ± SD	TVP+, mean ± SD	*P*-value
LA volume-i (ml/m^2)			
Preoperative	61.81 ± 29.46	66.65 ± 25.92	0.39
Follow-up	42.84 ± 22.16[a]	51.05 ± 23.63[a]	0.08
RA volume-i (ml/m^2)			
Preoperative	35.42 ± 14.43	40.77 ± 37.31	0.37
Follow-up	34.32 ± 16.26	33.63 ± 13.11	0.83
LVEDDi (mm/m^2)			
Preoperative	28.84 ± 4.39	28.82 ± 4.86	0.99
Follow-up	26.24 ± 3.96[a]	26.29 ± 3.33[a]	0.94
LVESDi (mm/m^2)			
Preoperative	18.99 ± 3.66	18.75 ± 4.26	0.76
Follow-up	19.56 ± 4.05	19.94 ± 3.76[a]	0.63
LVEDVi (ml/m^2)			
Preoperative	121.65 ± 32.40	123.47 ± 34.04	0.78
Follow-up	80.23 ± 72.21[a]	74.96 ± 23.81[a]	0.63
LVESVi (ml/m^2)			
Preoperative	50.43 ± 21.74	51.58 ± 18.52	0.77
Follow-up	36.76 ± 15.17[a]	39.34 ± 12.15[a]	0.36
EF			
Preoperative	0.59 ± 0.10	0.58 ± 0.09	0.57
Follow-up	0.49 ± 0.11[a]	0.47 ± 0.09[a]	0.22

[a]$P < 0.05$ compared the preoperative value.
EF: ejection fraction; LA: left atrium; LVEDDi: left ventricle end diastolic diameter index; LVEDVi: left ventricle end diastolic volume index; LVESDi: left ventricle end systolic diameter index; LVESVi: left ventricle end systolic volume index; RA: right atrium; SD: standard deviation; TVP: tricuspid valve annuloplasty.

Surgical outcomes

MV replacement was performed in 92 patients (47 TVP^- versus 45 TVP^+; p = 0.77) with resection of the posterior leaflet in 54 patients (22 TVP^- versus 32 TVP^+; p = 0.22). Artificial chordae were used in 33 patients, and a mix of other techniques were used, including commissurotomy (six patients), flip-over technique (two patients), papillary muscle re-implantation (one patient), and annular decalcification (five patients). Median mitral ring size was 32.8 ± 2.9. MV replacement was performed in six patients in the TVP^- and eight patients in the TVP^+ groups. A TVA was performed with a semi-rigid ring. Median ring size was 31.8 ± 1.3. In five patients in this group, the surgeon did not perform a TA; three cases were not done because it was at the end of a very long procedure already (double valve replacement with decalcification of the MV annulus and patch repair of the annulus), and in the other two, the surgeon was reluctant because the annulus size was normal, and he did not want to increase the complexity of the procedure.

Coronary artery bypass grafting (TVP^+ =15.1% versus TVP^- = 26.4%; p = 0.23), aortic valve repair (TVP^+=7.5% versus TVP^- =5.7%; p = 1) or replacement (TVP^+=3.8% versus TVP^- =1.9%; p = 1), and atrial fibrillation ablation (TVP^+=18.9% versus TVP^- = 13.2%; p = 0.6) were similarly performed in both groups. Cardiopulmonary bypass and clamp times (123 ± 35 and 100 ± 36 min, respectively [P = 0.01]) increased in the TVP^+ group.

Clinical and echocardiographic results

The median follow-up was 3.8 years (3–5.6 years). Thirty-day freedom from mortality was 98.11% ± 1.9% and 96.2% ± 2.6% in the TVP^- and TVP^+ groups, respectively (p = 0.57). Five-year freedom from cardiac-related mortality was also similar (89.7% ± 4.3% in the TVP^- group versus 94.1% ± 3.2% in the TVP^+ group [p = 0.9]). VO_2 max at one and three years (TVP^- 20.1 ± 7.6 versus TVP^+ 19.2 ± 8 ml/min/kg [p =0.22] and TVP^- 20.7 ± 5.2 versus TVP^+ 20.3 ± 5 ml/min/kg; p = 0.24, respectively) did not differ between groups. In the TVP^+ group, 96.4% of the patient population was free from NYHA > II versus 92.9% in the TVP^- group (p = 0.37).

At follow-up, five and seven patients presented moderate and severe TR, respectively. The freedom from moderate or more TR at five years was higher in the TVP+ group (100% versus 76.1% ± 6.9%; p < 0.01) as shown in Figure 1), and freedom from severe TR was also lower in TVP+ group (0% versus 87.4%)(Figure 2). Only one patient in the TVP^- group underwent repeat surgery on the TV for moderate regurgitation recurrence during a reoperation for a severe recurrence of MV insufficiency. Progression of FTR (defined as increase of > 3 mm VC between pre-operative and follow-up echocardiography examintions) occurred more frequently in the TVP^- group (17.6% versus 0%, p<0.01). Individual evolution of TR is presented in figure 3.

Figure 1. Kaplan–Meier curve for moderate or greater tricuspid regurgitation (TR).

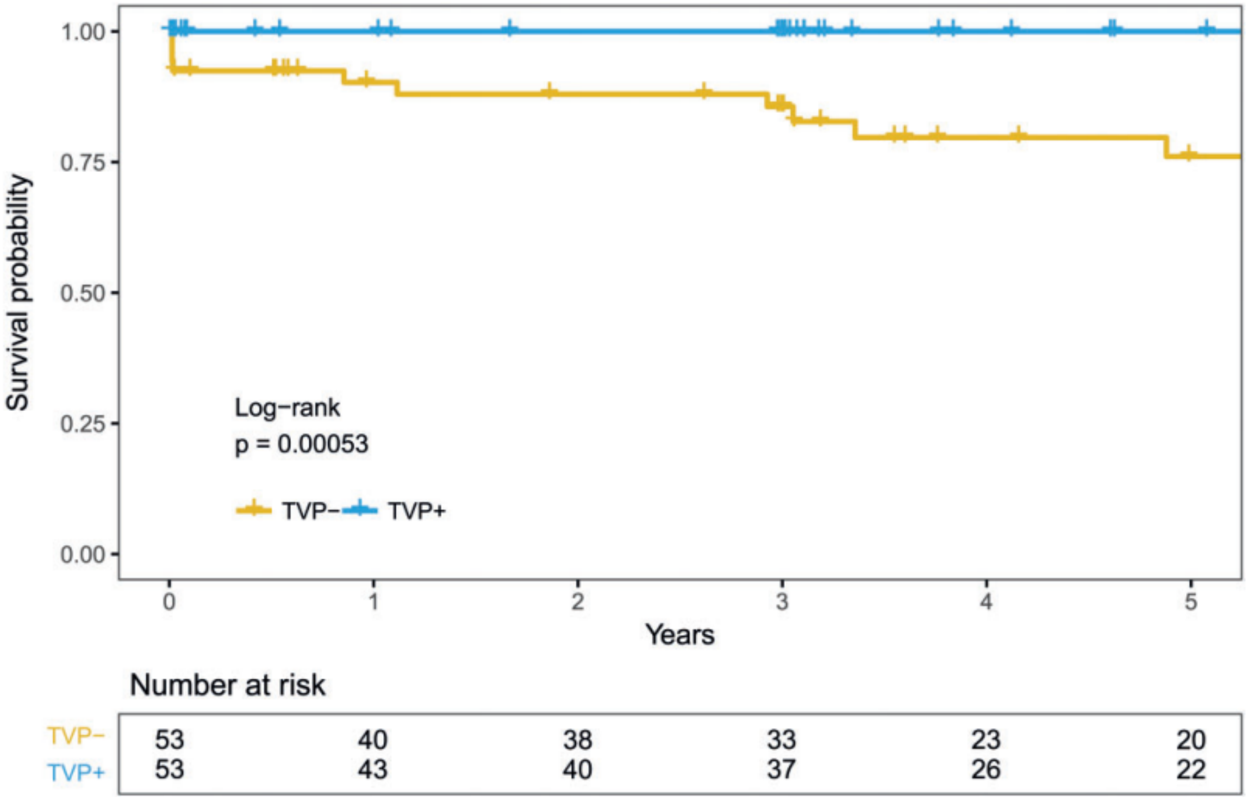


Figure 2. Kaplan–Meier curve for severe TR.

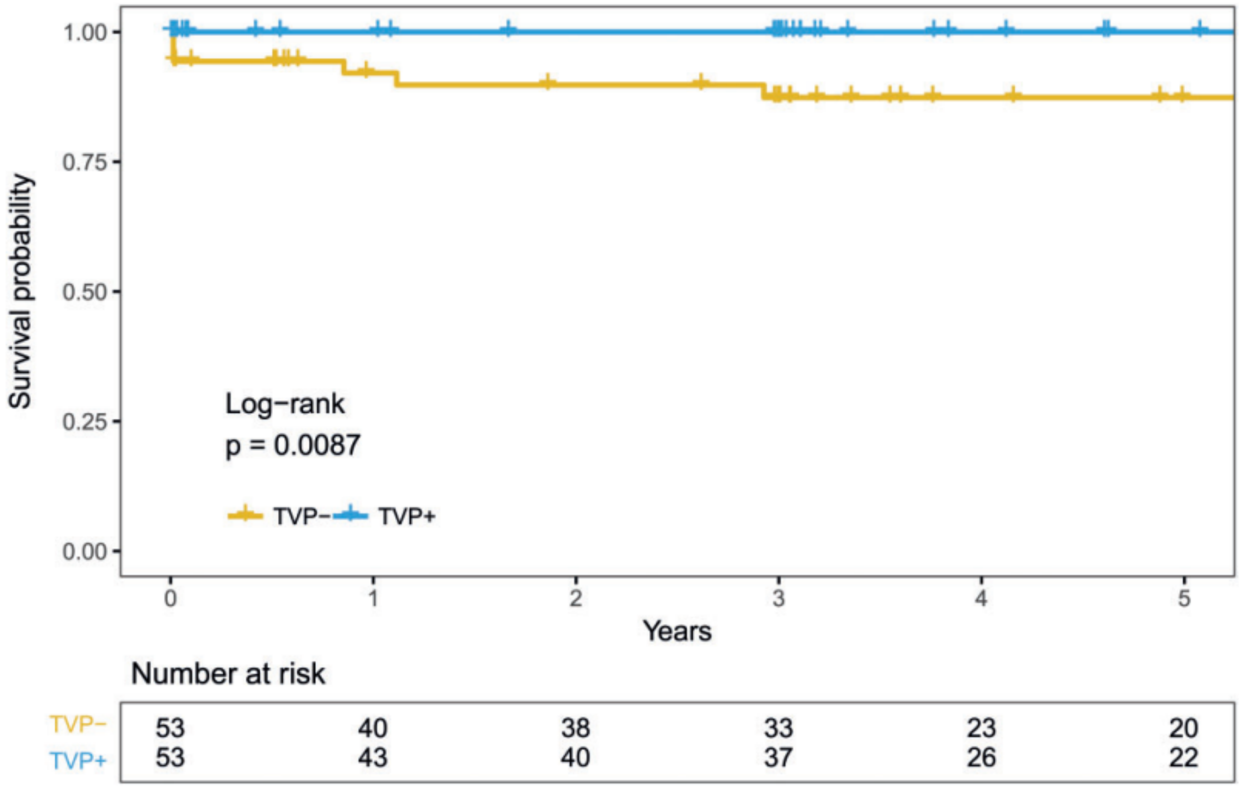
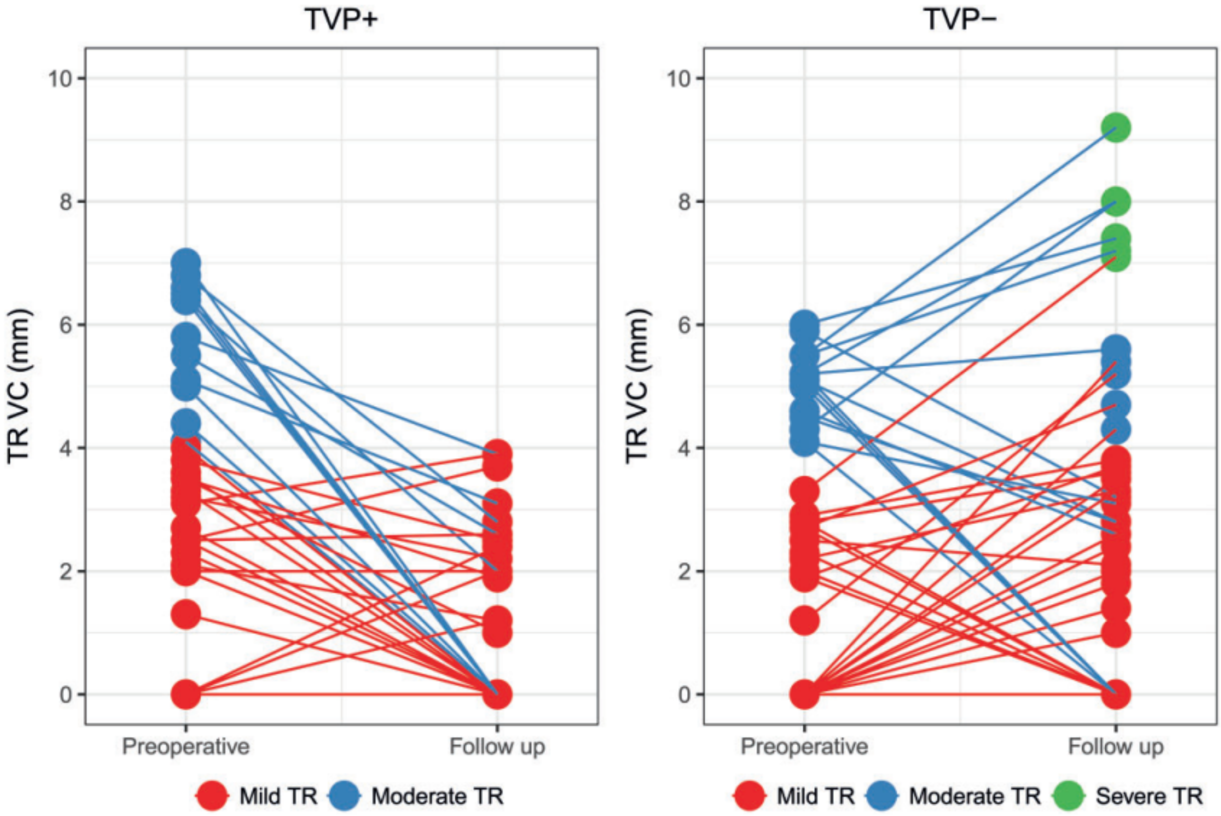


Figure 3. Plot of the TR vena contracta (VC) differences between pre-operative and follow-up periods per group.



Echocardiographic follow-up data are presented in Tables 3. LV and RV dimensions and functions did not differ between the groups, which was similar to that observed in the left and right atria. The pulmonary artery pressure measurement was available for 92 patients (46 in the TVP+ and 46 in the TVP- groups), and in the TVP+ group, this measurment was significantly reduced ($p < 0.01$) (Table 3).

Table 3: Echocardiographic data (preoperative vs follow-up) of the right ventricle and tricuspid valve

	TVP-, mean ± SD	TVP+, mean ± SD	*P*-value
RVEDAi (cm^2/m^2)			
Preoperative	12.76 ± 2.75	12.80 ± 2.82	0.95
Follow-up	12.96 ± 2.66	12.82 ± 2.76	0.81
RVESAi (cm^2/m^2)			
Preoperative	8.27 ± 2.44	8.31 ± 2.04	0.94
Follow-up	7.98 ± 1.83	8.88 ± 3.90	0.19
FAC (%)			
Preoperative	35.30 ± 11.74	34.92 ± 9.69	0.87
Follow-up	38.03 ± 7.56	35.58 ± 7.51	0.14
RV basal diameter-i (mm/m^2)			
Preoperative	23.93 ± 4.77	24.38 ± 4.34	0.65
Follow-up	25.87 ± 3.52	23.59 ± 4.52	0.01
RV mid-diameter-i (mm/m^2)			
Preoperative	19.33 ± 4.62	19.69 ± 3.72	0.69
Follow-up	19.54 ± 3.63	19.86 ± 3.97	0.71
RV long axis (mm)			
Preoperative	71.68 ± 9.98	70.12 ± 8.34	0.44
Follow-up	70.72 ± 8.98	71.78 ± 11.13	0.63
TR VC width (mm)			
Preoperative	2.20 ± 2.22	2.55 ± 2.37	0.43
Follow-up	2.44 ± 2.62	0.74 ± 1.23	<0.01
TAPSE (mm)			
Preoperative	1.96 ± 0.56	1.99 ± 0.68	0.76
Follow-up	2.11 ± 4.18	1.12 ± 0.49	0.12
PAP systolic (mmHg)			
Preoperative	37.10 ± 12.47	37.50 ± 18.37	0.90
Follow-up	29.49 ± 12.33[a]	22.96 ± 14.38[a]	0.02
TA end diastolic (mm)			
Preoperative	39.55 ± 5.41	40.14 ± 5.76	0.60
TA end systolic (mm)			
Preoperative	34.50 ± 5.38	35.51 ± 5.94	0.48

[a]$P < 0.05$ compared the preoperative value.

FAC: fractional area change; PAP: pulmonary artery pressure; RV: right ventricular; RVEDAi: right ventricle end diastolic area index; RVESAi: right ventricle end systolic area index; SD: standard deviation; TA: tricuspid annulus; TAPSE: tricuspid annulus plane excursion; TR: tricuspid regurgitation; TVP: tricuspid valve annuloplasty; VC: vena contracta.

Predictors of TR

Recurrence of MR (defined as VC more than 7 mm or effective regurgitant orifice area [EROA] ≥ 0.4 cm^2 or regurgitant volume ≥ 60 ml) or MV reoperation at five years was also similar (TVP^- =9.4% ± 1.6% versus TVP^+ =5.6% ± 1%; p = 0.29) and also mean gradient across the MV (TVP^- =3.6 ± 2.4 mmHg versus TVP^+ =3.5 ± 1.3 mmHg; p = 0.95)

Cox analysis identified that TA (p =0.04) and pre-operative MR VC (p=0.04) influence post-operative TR, whereas pre-operative TA diameter (systolic and diastolic) did not influencethis parameter..

MRI data

Data obtained from the cardiac MRI are presented in the Table 4. Pre- and post-opertaive RV volumes and functions were similar in both groups. The differential in terms of RV end-diastolic (TVP^- = 5.8 ± 31.5 versus TVP^+ =19 ± 39.4; p = 0.4) and end-systolic volumes (TVP^- =5.8 ± 18.8 versus TVP^+ =16.8 ± 27.1; p = 0.5), stroke volumes (TVP^- =3.2 ± 19.7 versus TVP^+ =6.7 ± 27.5; p = 0.4) and EFs (TVP^- =3.2 ± 9.6 versus TVP^+ = 2.7 ± 11.8; p = 0.8) were also similar.

Table 4: Magnetic resonance imaging measurements

	Preoperative, mean ± SD			Postoperative, mean ± SD		
	TVP-	TVP+	*P*-value	TVP-	TVP+	*P*-value
RVEDV (ml)	161.82 ± 52.84	173.12 ± 58.62	0.65	157.60 ± 37.72	153.15 ± 34.03	0.78
RVEDVi (ml/m^2)	91.80 ± 24.73	90.47 ± 29.72	0.95	85.58 ± 17.01	73.62 ± 10.23	0.17
RVESV (ml)	83.97 ± 35.91	85.96 ± 36.61	0.90	75.66 ± 27.41	72.74 ± 22.54	0.79
RVESVi (ml/m^2)	48.01 ± 17.89	49.64 ± 28.69	0.93	41.39 ± 13.28	34.01 ± 8.34	0.28
RVSV (ml)	77.85 ± 20.88	87.16 ± 33.61	0.49	81.93 ± 19.57	80.41 ± 12.89	0.82
RVSVI (ml/m^2)	43.80 ± 9.17	40.83 ± 11.07	0.70	44.19 ± 9.87	39.60 ± 1.89	0.13
RVEF (%)	49.61 ± 7.22	50.90 ± 9.61	0.74	52.99 ± 9.67	53.27 ± 4.87	0.93

RVEDV: right ventricle end diastolic volume; RVEDVi: right ventricle end diastolic volume index; RVEF: right ventricle ejection fraction; RVESV: right ventricle end systolic volume; RVESVi: right ventricle end systolic volume index; RVSV: right ventricle stroke volume; RVSVi: right ventricle stroke volume index; SD: standard deviation; TVP: tricuspid valve annuloplasty.

Discussion

The main finding of the current study indicates that concomitant TA prevents TR recurrence in patients with less than severe TR who are referred for MV surgery. TA dimensions were not identified as predictors of TR recurrence but pre-operative MVR and TA were. Whether the use of a prophylactic TVA at the time of MV surgery is necessary is presently a highly debated topic. After the seminal paper by Dreyfus [4], who defined annular dilatation as ≥ 70 mm distance from the commissure between septal and anterior leaflets to the base of the posterior leaflet, several others authors confirmed annular dilatation as a predictor of TR recurrence. These authors also reported the use of a prophylactic TA led to a reduction in the risk of TR and improved RV remodelling. Van deVeire [7] measured the TA in a 4-chamber view from a transthoracic echocardiography and defined tricuspid dilatation as ≥ 40 mm. Using this cut-off, RV reverse remodelling and TR grade improvement (1.6 ± 1 versus 0.9 ± 0.6 on a scale of 1 to 4) was observed at the 2-year follow-up in patients with TA dilatation who underwent concurrent TVA during surgery for degenerative or functional MV disease. Those findings were confirmed by Adams et al. [6]. After treating a group of 645 patients for degenerative disease, TVA was performed in any case of moderate TR and annular dilatation (≥ 40mm). It was also performed in cases of equivocal findings on the basic of direct assessment and comparison of the anterior/posterior leaflet surface area with the annulus size and presence of additional risk factors (such as atrial fibrillation, PH, or RV dysfunction as found in 301 patients). With this more inclusive policy, 65% of the patients underwent a TVA. They observed that the RV function recovery occurred more rapidly in the TVA group and that TVA was the main independent positive predictor of late RV recovery in the subgroup of patients with pre-discharge RV dysfunction by five years post-operatively even if the TR recurrence reduction was not really significant (freedom from moderate TR of 97% versus 91%; p = 0.07). They reported an improvement in PAH as we did. The possible hypothesis concerning that finding is a correlation with RV function, which had improved in the paper from Adams group. These findings were also influenced by the recent European guidelines [9], which sugges that a pre-operative echocardiographic TV annulus ≥ 40 mm is an indication for TA (class IIa, level C), supporting the use of this marker as early predictor of right chamber remodelling before appearance of TR. Our study confirmed this finding only partially; we reported an increase in TR recurrence without annuloplasty, but annular dilatation did not predict this complication, and the RV dimension and function did not improve.

In contrast, David [18] recently stated that TR recurrence is uncommon after MV repair for degenerative diseases, accounting for 13.6% of the patients treated for degenerative disease at 15 years, but 11 of them already had undergone TVA. Recurrence was also associated with advanced age at surgery, unrepaired pre-operative moderate/severe TR, and the development of post-operative MR. Similarly, Yilmaz and colleagues [19] from the Mayo Clinic examined the outcomes of 693 patients who had undergone isolated MV repair for MR due to MV prolapse. They observed a significant reduction in the overall grade of TR within the first three years but found a slight increase after five years. Female sex, pre-operative atrial fibrillation (AF), and diabetes mellitus were independent risk factors for increased TR over time. A more recent evaluation of this issue at that institution confirmed that MV repair in addition to MV replacement led to a reduction in post-operative TR grade, and the development of new TR was uncommon [20]. Developemnt of new TR was associated with female gender, left atrial dimension, and abnormal RV systolic pressures. More recently, Sordelli [21], used 3-dimensional (3D) imaging and failed to show a correlation between the diameters of the TV annulus (anteroposterior and septolateral) and TR development after MV repair for degenerative diseases. The authors concluded that "newly developed significant TR is a rare event after successful repair of degenerative MR." Again, our findings only partially support this part of their discussion, confirming that a single measurement of 40 mm as the cut-off point of dilated TV annulus is probably inappropriate and It may be too large for patients with small TV leaflets (such as patients with MR due to fibroelastic deficiency) and too small for patients with MR due to advanced myxomatous degeneration. Furthermore, 2D measurements are not adequate to quantify tricuspid annular dilatation; thus, only 3D images should be used. The ability to predict TR recurrence should be researched with respect to several factors: (1) preload (annular dilatation, atrial enlargement and atrial fibrillation); (2) afterload (recurrence of MR, pulmonary hypertension); and (3) RV function (which, unfortunately, is not appropriately defined). All of these parameters were describe in the previous papers as major predictors of TR.

Limitations in our study was the relative small sample size, which was probably too small to draw some conclusions about the correlation of recurrent TR and VO_2 max. In addition, the data concerning RV volumes and function are limited (from only 30 patients). The median follow-up was nearly four years; therefore, longer follow-up periods are desired to confirm the preliminary results also because mean age of the patients was 62 years.

In conclusion, our study confirmed that TR recurrence after MV surgery for degenerative and rheumatic disease can be improved by prophylactic tricuspid annuloplasty and improvements in a patient's pulmonary hypertension at follow-up but did not demonstrate a difference in reverse remodelling or clinical benefits. This article reinforces the concept that FTR cannot be limited to only TR or annular dilatation because many other factors play a major role in FTR aetiology, and we are still not addressing them properly. We hope that the ongoing randomized, controlled clinical trial will settle this controversy. Such a trial is currently enrolling study participants. The Cardiothoracic Surgical Trials Network will randomly assign 400 patients with degenerative MV disease with one of two issues: (1) moderate TR or (2) TA dilatation (≥40 mm) and TR graded as trace or mild to undergo either MV surgery alone or MV surgery plus a rigid, nonplanar, undersized TVA.

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Comparison of 3D Echo and *In-Vivo* Analysis of the Tricuspid Valve During Mitral Valve Surgery.

Comparison of 3D Echo and *In-Vivo* Analysis of the Tricuspid Valve During Mitral Surgery. 3D-Echo versus *In Vivo* Analysis of the Tricuspid Valve

Article Information

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Abstract

Background: The tricuspid valve (TV) is a complex three-dimensional (3D) structure. Two- or three-dimensional echocardiography is the gold standard for evaluating valve function and anatomy. The aim of our study was to compare *in vivo* analysis with 3D echocardiography tricuspid valve (TV) measurements in patients treated for mitral valve (MV) disease.

Methods: Among the 139 patients treated for MV disease, 37 underwent an intra-operative evaluation using 3D trans-esophageal echocardiography. After exposure of the valve, we took several pictures to obtain annular and leaflet measurements. We traced the echocardiographic annular measurements (area, perimeter, septal anterior, and latero-lateral diameters) during six different moments of the cardiac cycle that included early, mid, and late systole and diastole. Leaflet lengths and areas were measured only during end-systole and diastole. Based on the intra-operative pictures, we obtained annular and leaflet measurements and compared them to echocardiographic findings using Pearson's correlation test.

Results: Significant correlations were found between 3D echocardiographic and *in vivo* measurements in terms of valve areas and perimeter ($p < 0.01$; $r = 0.77$ and $p < 0.01$; $r=0.61$, respectively) while diameters showed a moderate correlation. Correlations of leaflet measurements were poor (R: 0.51–0.61). Multivariate linear regression analysis identified annulus areas and tenting height ($p = 0.03$ and 0.04, respectively) as significant predictors of TVR.

Conclusion: Our study demonstrated that annulus area and perimeter correlate better than diameters for measuring the TA and have significant influence on functional TR. Leaflet analysis remains limited. Further studies will identify their impact on follow-up recurrence of FTR.

Keywords: 3D Echocardiography; Mitral valve disease; Intraoperative; Tricuspid

Abbreviations:

FTR=functional tricuspid regurgitation, TA= tricuspid annulus, TV= tricuspid valve, 2D 3D= two and three dimensional, TEE= trans esophageal echocardiography, TTE= trans thoracic echocardiography, ES= early systole, MS= mid systole, LS= late systole, ED= Early diastole, MD= mid diastole, LD=late diastole, SA= septal anterior, LL= latero lateral, HTA= Arterial Hypertension, COPD== Chronic Obstructive Pulmonary Disease, PVD= Peripheral Vascular Disease, CVA= Cerebral Vascular Accidents, BSA= Body Surface Area

1. Introduction

Recent valvular treatment guidelines assign a Class IIa recommendation for tricuspid valve (TV) repair in the presence of tricuspid annulus (TA) dilatation irrespective of TR severity [1]. Correct evaluation of the TA is thus of paramount importance for adequate surgical indication. Nowadays, the decision to intervene is usually based on the measurement of TA diameter obtained by transthoracic or transesophageal evaluation. Although two-dimensional (2D) echocardiography is the standard technique for measuring aortic and mitral annular dimensions, it is also most likely appropriate for assessing TV dimension. Indeed, compared to these two valves, the tricuspid valve has a much more complex non-circular geometry [2]. This phenomenon is even exaggerated in the presence of functional tricuspid regurgitation (FTR) as the anterior and posterior parts of the annulus tend to dilate more than the septal part. This difference makes it difficult to accurately measure tricuspid annular dimensions from a single 2D echocardiography cross section. 3D echocardiography has been shown to overcome the limitations of 2D echocardiography in non-circular objects. Accordingly, the aim of the present study was to compare 2D and 3D measurements of the TA with their intra-operative equivalents. We also compared 3D measurements of valve leaflet areas and lengths with those obtained during surgery.

2. Materials and Methods

Between May 2009 and May 2011, 139 patients who underwent mitral valve (MV) surgery were screened for inclusion into a prospective randomized trial addressing prophylactic tricuspid annuloplasty (TVA) [2], among which 59 ultimately underwent combined TV annuloplasty. The surgical procedures and techniques have been previously described [2]. The study protocol was approved by our institutional review board, and all patients gave their written informed consent prior to inclusion into the study.

2.1 Pre-operative transthoracic 2D-echocardiography

Standardized pre-operative transthoracic echocardiogram (TTE) examinations were acquired according to established guidelines using the iE33 ultrasound systems= (Philips Medical Systems, Andover, Massachusetts) equipped with a 3.5/1.75-MHz phased-array transducer. Images were stored on a XCELERA 2.1 PACS server (Philips Medical Systems, Andover, Massachusetts) for off-line analysis. Four chamber views centred on the right ventricle (RV) were used to evaluate RV dimensions and function and to measure TA dimensions. Zoomed-in 2D color-doppler images, centred on the TA plane were used to measure the vena contracta (VC) of the TR jet in a 4 chamber view. Based on these measurements, TR severity was categorized as mild (VC < 3mm) , moderate (VC between 3 and 6 mm) and severe (VC ≥ 7mm).

2.2 Intra-operative transesophageal 2D- and 3D-echocardiography

Experienced cardiologists or anaesthesiologists performed all TEE examinations after induction of general anesthesia prior to cardiopulmonary bypass using an iE-33 ultrasound system equipped with an X7-2t TEE probe (Philips Medical Systems, Andover MA). Standard 2D echocardiography of the TV (at an average frame rate of 55 to 60 Hz) were acquired from the 4-chamber, right ventricle inflow–outflow, and transgastric right ventricle inflow views [3] to measure the TA diameter at end-systole and end-diastole. Zoomed-in 3D echo images of the TA were then acquired from a mid-oesophageal 4 chamber view, during brief periods of breath hold without electrical interference or patient movement over 4 to 8 cardiac cycles. Great care was taken to include the entire TA within the 3D volume. 3D images were analysed off-line using the Image Arena software (Tom-Tec Corporation GmBH, Munich, Germany) and the 4D mitral valve analysis package. This package allows for the semi-automatic identification and measurements of the mitral annulus and leaflets throughout the entire cardiac cycle; manual adjustments were made if needed. For annular measurements, only six specific time-points were analysed: 1) early systole (ES): first frame after closure of the tricuspid valve; 2) late systole (LS): last frame prior to tricuspid valve opening; 3) mid systole (MS): midpoint between ES and LS; 4) early diastole (ED): first frame after valve opening; 5) late diastole (LD): the last frame prior to complete tricuspid valve closure; and 6) mid diastole (MD): midpoint between ED and LD. For each of these prespecified time points, the software automatically generates the following measurements: 1) maximal diameter from the septum to the anterior leaflet (septal-anterior diameter); 2) the lateral-lateral diameter (the largest diameter perpendicular to the previous); 3) the annulus area (2D and 3D); and 4) the annulus perimeter (2D and 3D) as shown in Figure 1. Leaflet measurements were performed at end-systole and mid-diastole. The software generated the area and maximal length of two leaflets, the septal, and the combination of the anterior and posterior leaflets. No attempt to quantify FTR was made intra-operatively as TR severity is notably underestimated under general anaesthesia.

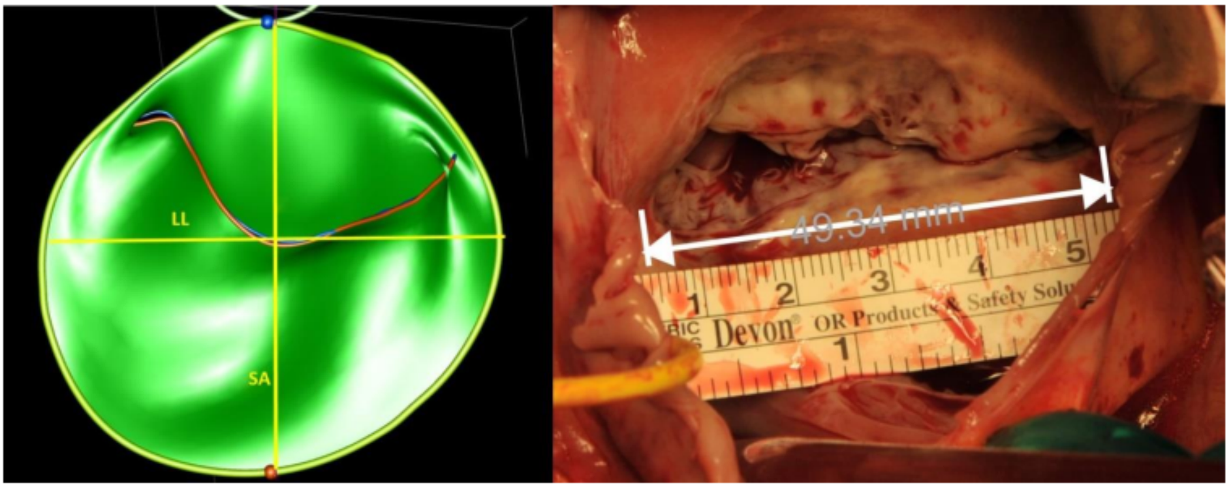

Figure 1: Example of the three-dimensional (3D) echocardiographic reconstruction obtained from the TOMTEC software and the intraoperative pictures to evaluate in vivo measurements.

2.3 Intra-operative pictures

After right atriotomy, the TV was exposed using a standard atrial retractor (Cosgrove Valve Retractor System – Kapp Surgical Instrument Inc.) in an attempt to maximize the exposure of the tricuspid annulus and leaflets. We positioned a sterile ruler onto the annulus for calibration (Figure 1). We first photographed the valve without leaflet retraction to visualize the annulus. Thereafter, we exposed each leaflet by means of a slight retraction to take selective images. We use ImageJ, an open source image processing software designed for scientific multidimensional images, to perform the post hoc data processing. Similar to the 3D-echo evaluation, four annular dimensions were selected: 1) maximal diameter from the septum to the anterior leaflet (septal-anterior diameter); 2) the latero-lateral diameter (the largest diameter perpendicular to the previous); 3) the annulus area; and 4) the annulus perimeter. We traced the leaflet area, (trace of the leaflet until the origin of the chordae) and the leaflet length (maximal distance between the free margin and the base). Again, we combined the leaflet area of the anterior and posterior leaflets in order to compare their measurements with the corresponding 3D echo images.

2.4 Statistical analyses

All analyses were conducted using the RStudio software (Version 1.0.153–© 2009–2017 RStudio, Inc.). Continuous variables were expressed as mean ± standard deviation, categorical variables were expressed as counts and percentages, and follow-up times were expressed as median and range. Continuous variables were compared using the Student's t- or Mann–Whitney U-test. Repeated measure analysis of variance (ANOVA) was used to compare TA 3D echo measurements at each pre-specified time point. Categorical variables were compared using the $\chi 2$ or Fisher's exact test when appropriate. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. Agreement between methods of TA measurements was assessed using the Bland–Altman method [4]. Multivariate regression analysis was used to identify significant predictors of pre-operative TR. We used a multi criteria method to identify significant parameters in the multivariate analysis based on the Akaike information criterion (AIC), Mallows' Cp, and adjusted R^2. The best combination of those parameters was used to construct the final model. Variance inflation factors (VIF) using a cut-off of 10 was used to check for multicollinearity. Receiver operating characteristic (ROC) curves were used to calculate areas under the curves (AUC) and to derive optimal cut-off values. Intra- and inter-observer agreements for annular measurements were tested using the Bland–Altman method in addition the intra-class correlation coefficients.

3. Results

The final study population consisted of 37 patients in whom both intra-operative pictures and a complete 3D TEE examination of the tricuspid valve were available. Figure 2 shows the flowchart of patient selection. Table 1 shows the demographic and clinical characteristics of the study population categorized according to the baseline severity of FTR.

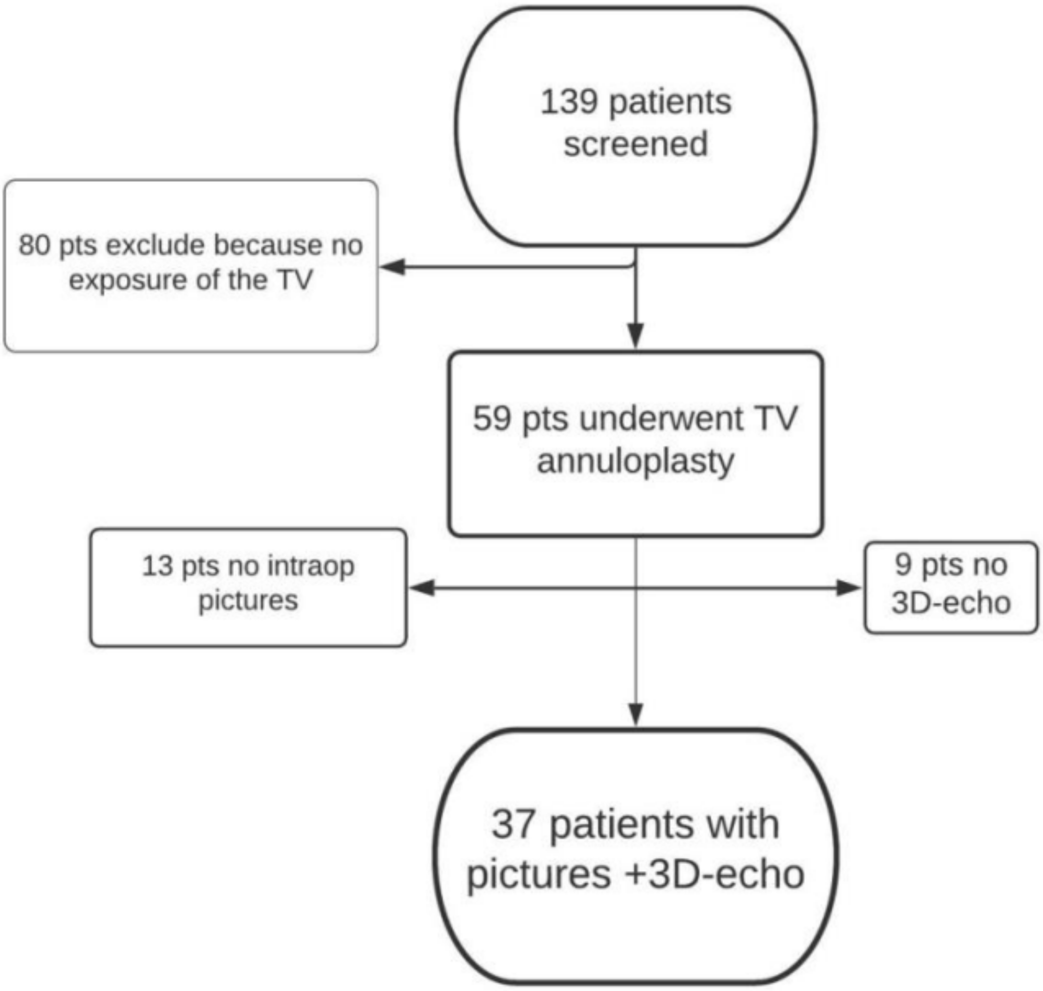

Figure 2: Flowchart of the patients selection.

	[ALL] N=37	≤ Mild N=18	Moderate N=8	Severe N=11	p value
Age	63.0±15.9	58.8±12.2	65.0±22.7	68.5±15	0.27
Male	17 (45.9%)	9 (50%)	4 (50%)	4 (36.4%)	0.76
HTA	18 (48.6%)	6 (33.3%)	5 (62.5%)	7 (63.6%)	0.19
Diabetes	5 (13.5%)	1 (5.6%)	2 (25%)	2 (18.2%)	0.39
Smoke	4 (10.8%)	2 (11.1%)	1 (12.5%)	1 (9.1%)	1
BPCO	1 (2.7%)	0 (0%)	1 (12.5%)	0 (0%)	0.22
Kidney Failure	3 (8.1%)	0 (0%)	1 (12.5%)	2 (18.2%)	0.12
PVD	1 (2.7%)	0 (0%)	0 (0%)	1 (9.1%)	0.51
SR	17 (45.9%)	11 (61.1%)	2 (25.0%)	4 (36.4%)	0.22
CVA	1 (2.7%)	0 (0%)	1 (12.5%)	0 (0%)	0.22
Carpentier class:					0.31
I	1 (2.7%)	0 (0%)	0 (0%)	1 (9.1%)	
II	23 (62.2%)	12 (66.7%)	5 (62.5%)	6 (54.5%)	
IIIa	11 (29.7%)	6 (33.3%)	3 (37.5%)	2 (18.2%)	
IIIb	2 (5.4%)	0 (0%)	0 (0%)	2 (18.2%)	
BSA	1.9±0.3	1.9±0.3	1.9±0.2	1.9±0.3	0.97

Table 1: Patient demographic characteristics in function the degree of functional tricuspid regurgitation.

HTA= Hypertension; COPD== Chronic Obstructive Pulmonary Disease; PVD= Peripheral Vascular Disease; CVA= Cerebral Vascular Accidents; BSA= Body Surface Area

3.1 Annular dimension

Table 2 compares direct intra-operative measurements of the TA with similar measurements based on 2D and 3D echo. As shown at each time point, both 2D and 3D echos overestimated the intra-operative septal-anterior diameters, while at the same time it underestimated both the latero-lateral diameters, and perimeter. In contrast, annular areas were similar between 3D echo and those obtained during surgery. As shown in figures3, intra-operative surgical annular dimensions correlated well with those measured by 3D echo. Correlations with 2D echo were not as accurate (Figure 4).

	SA diam (mm)	**LL diam (mm)**	**Area (cm²)**	**Perimeter (cm)**
In vivo Measurement	30.1±7.3†	42.9±8.3†	10.2±4.5	12.2±2.4†
3D TEE Measurement				
Early-systole	33.1±7.9	34.2±9.3	9.53±4.8	11.2±2.7
Mid-systole	33.2±8.2	34.4±8.8	9.62±4.6	11.2±2.7
Late-systole	32.9±8.1	34.4±8.3	9.56±4.5	11.2±2.5
Early-diastole	32.9±8*	35.1±8.7	9.85±4.6	11.4±2.5
Mid-diastole	33.8±8.1	34.9±8.6*	9.96±4.6*	11.5±2.5*
Late-diastole	33.3±8.4	34.4±8.8	9.66±4.7	11.3±2.6

Table 2: Annular measurements

SA= Septal-anterior; LL= Latero-lateral; diam= diameter; TEE= Trans Oesophageal echocardiography.

* = Highest correlation between surgical and 3D TEE measurement;

†= significant (p value<0.05) difference compare the surgical measurement to 3D measurement for each time points

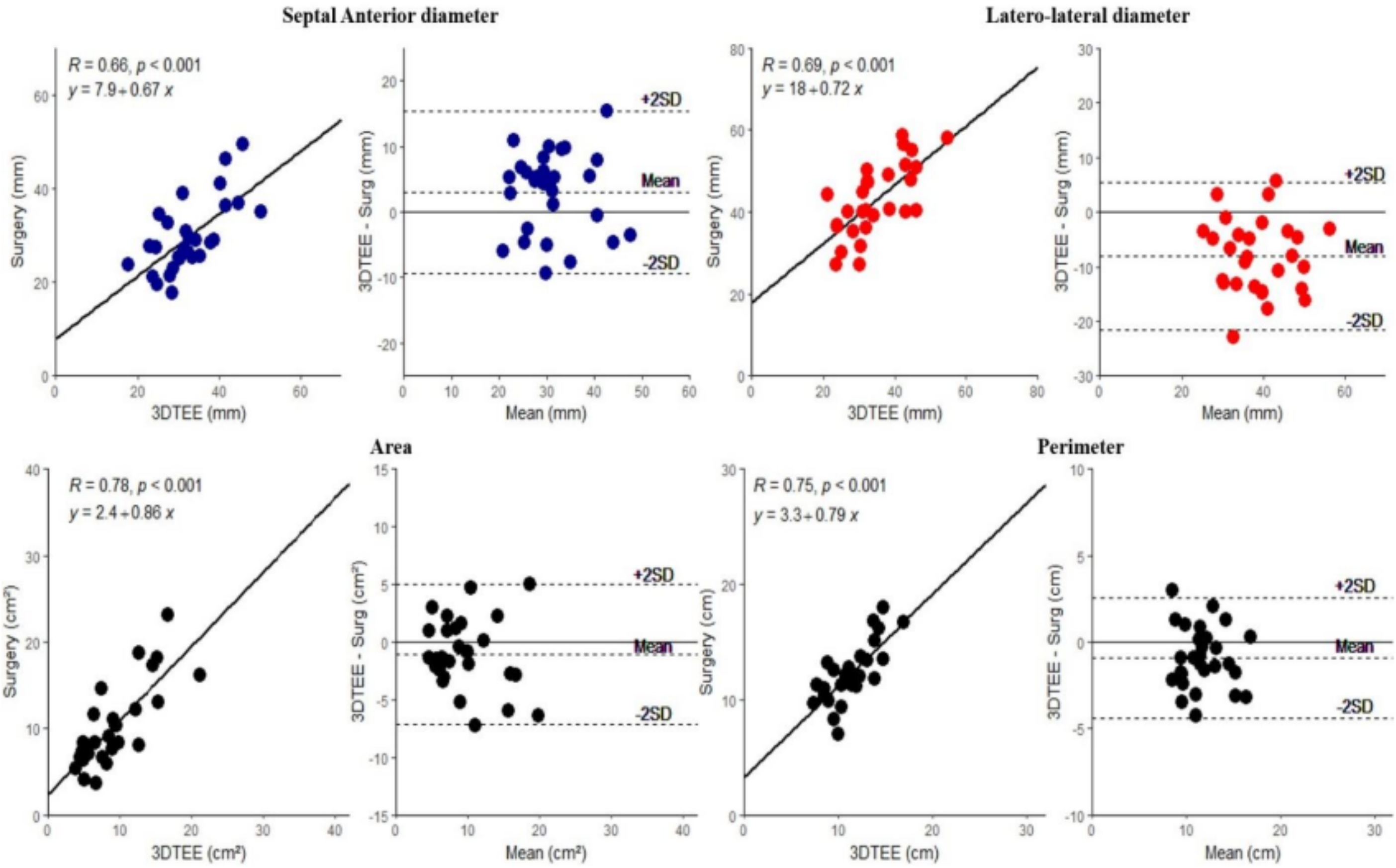

Figure 3: Linear correlation and Bland-Altman plots (the dashed lines represent the mean and the upper and lower lines ± 2 SD) of the annular measurements comparing Surgery to 3D echocardiography.

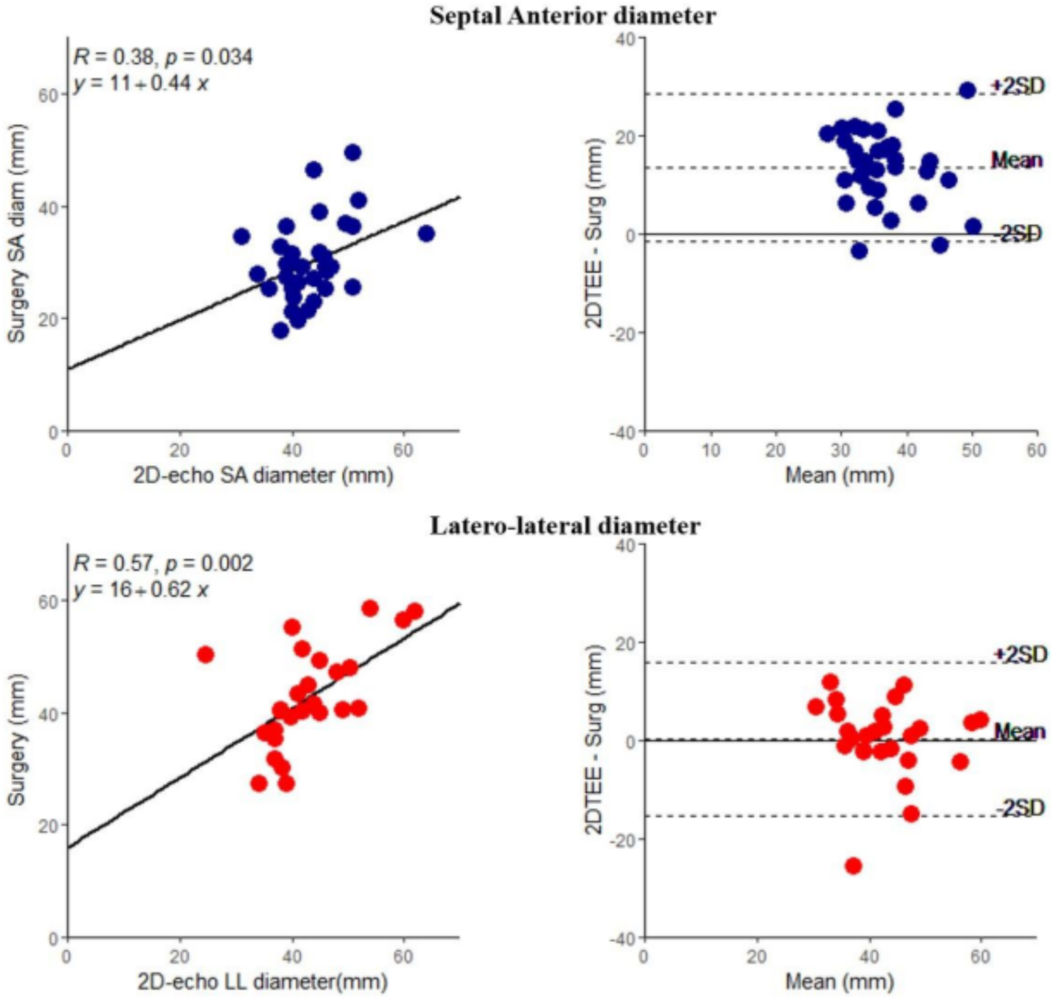

Figure 4: Linear correlation and Bland-Altman plots (the dashed lines represent the mean and the upper and lower lines ± 2 SD) of the annular measurements comparing Surgery to 2D echocardiography.

3.2 Leaflet dimensions

As shown in Table 3, the systolic area of the septal leaflet was found to be similar between the surgical and 3D echo measurements, whereas the diastolic area, septal length, and combined area of the anterior and posterior leaflets were significantly different. Correlation coefficients between leaflet measurements ranged from 0.53 to 0.62 (Supplementary material - Figure 1).

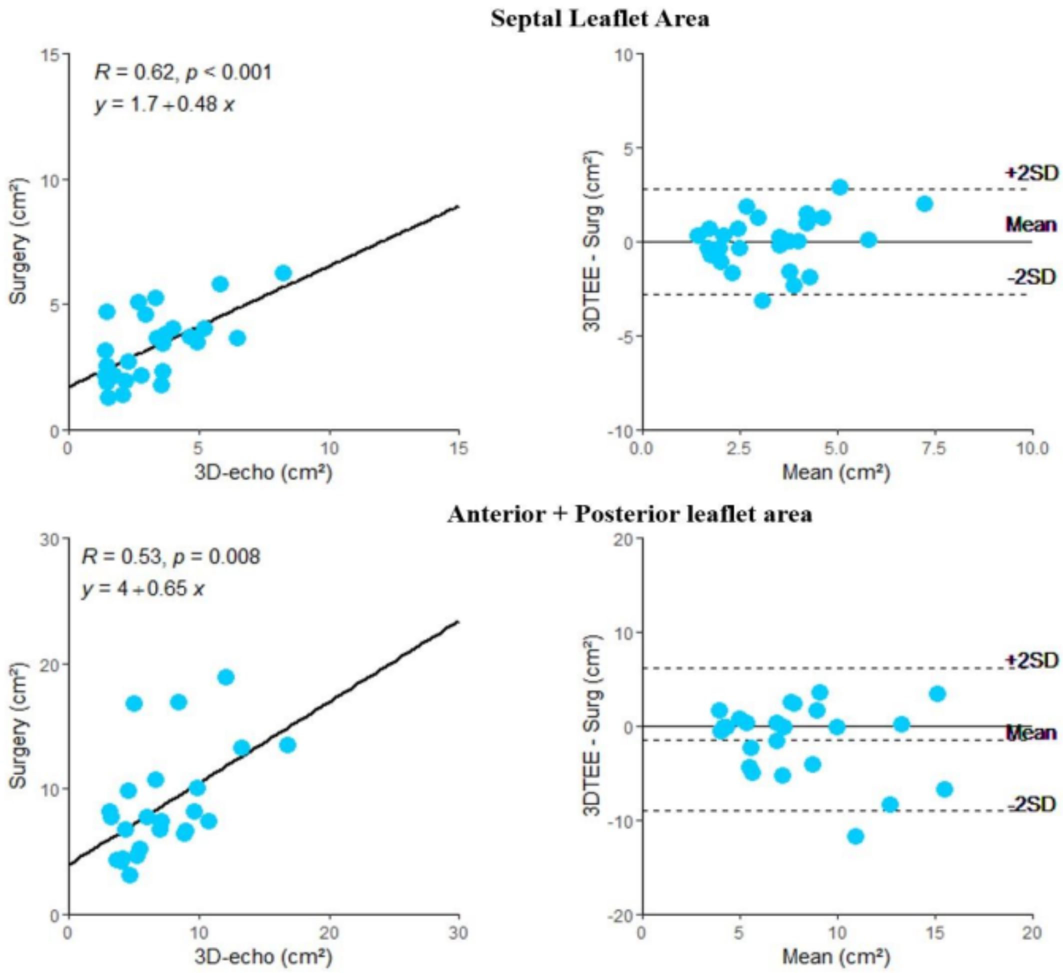

Figure 1: Linear correlation and Bland-Altman plots (the dashed lines represent the mean and the upper and lower lines ± 2 SD) of the leaflet measurements.

	SL area	SL length	A+P area
In vivo Measurement	3.2±1.3	1.7±0.5	8.5±4.1
3D TEE Measurement			
Systolic	3.8±2.7	1.5±0.6†	7±3.3†
Diastolic	4.6±2.5†	1.4±0.4†	9.6±5.5†

Table 3: Leaflet measurements

SL= Septal Leaflet; A+P = Anterior + Posterior Leaflet; TEE = Trans oesophageal echocardiography;

†= significant p value (< 0.05) comparing TEE to the surgical measurement.

3.3 Relationship with FTR

Table 4 shows the univariate and multivariate determinants of pre-operative FTR. Multivariate linear regression analysis identified 3D echo area and tenting height as independent predictors of pre-operative TR. As shown in Table 5 (Supplementary material Figure 2), an ROC analysis was used to identify the best cut-off values for the entire model in addition to each of its individual components and to calculate their capability to predict severe pre-operative FTR. As shown, pre-operative FTR was best predicted by the multivariate model (area under the curve [AUC] = 0.96; Sensitivity = 100%, Specificity = 88%) followed by 3D annular area (AUC = 0.79; Sensitivity = 81%, Specificity = 69%) and tenting height (AUC = 0.86; Sensitivity = 72%, Specificity = 92%). Interestingly 2D annular diameter was also found to be predictive for severe pre-operative FTR (AUC = 0.72; Sensitivity = 50%, Specificity = 81%) albeit less significantly than 3D echo measurements. The intra- and inter-observer variability for the annular measurements is shown in table 6. For both surgical and 3D TEE measurements, the inter- and intra-observer reproducibility was found to be reliable for areas and perimeters but less so for linear diameters.

	Univariate analysis			**Multivariate analysis**		
	Estimate	**Std.Error**	**P.Value**	**Estimate**	**Std.Error**	**P.Value**
Tenting.Height	0.85	0.12	<0.001	0.62	0.26	0.024
RV diastolic area	0.29	0.07	<0.001			
ES.Circumference	0.96	0.24	<0.001	7.17	1.63	0.01*
ES - LL diameter	3.19	0.82	<0.001			
LS.SA- Diameter	2.81	0.8	0.001			
LS. 3D Area.	0.47	0.14	0.001	11.71	4.18	0.01
RV. Basal diameter.	0.22	0.06	0.002			

Table 4: Results from Uni and Multivariate regression analysis for the preoperative FTR.

RV= right ventricle; ES=Early Systole; LL= Latero-lateral; LS= Late Systole; SA=Septal Anterior;

*After control for multicollinearity Circumference was exclude by the final model.

	Threshold	Sensitivity	Specificity	Accuracy
Full model	6.7	1	0.88	0.92
3D Circumference	10.8	0.82	0.69	0.78
3D Area	9	0.82	0.69	0.78
Tenting Heigth	4.1	0.73	0.92	0.81
2D-echo SA diam	42.5	0.5	0.8	0.75

Table 5: Cut-off results from the ROC analysis

3D= 3 dimensional; 2D= 2 dimensional; SA= Septal Anterior

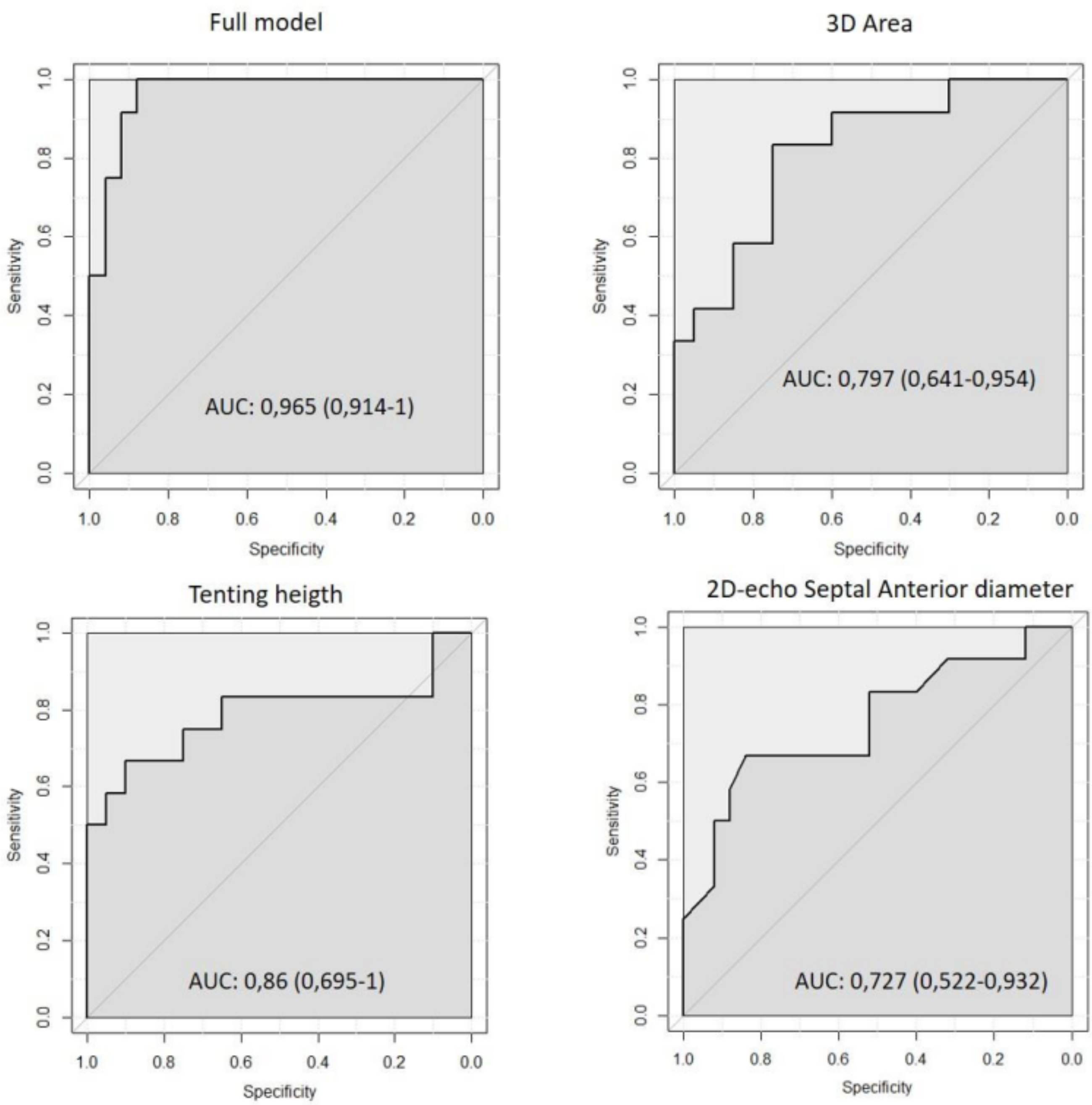

Figure 2: ROC analysis for predictor of preoperative TR.

	Intra observer variability ICC	Inter observer variability ICC
In vivo:		
Area	0.85 (0.74-0.91)	0.81 (0.73-0.91)
3D TEE:		
Area	0.89 (0.75-0.95)	0.81 (0.59-0.92)
Perimeter	0.87 (0.725-0.95)	0.80 (0.58-0.91)
SA diameter	0.81(0.58-0.92)	0.72 (0.43-0.88)
LL diameter	0.79 (0.56-0.91)	0.59 (0.22-0.81)

Table 6: Intra and intra observer variability.

ICC= Intra Class Correlation: 3D= 3 dimensional; TEE=Trans oesophageal echocardiography; SA= Septal Anterior; LL= Latero-lateral

4. Discussion

The aim of the present study was to compare *in vivo* 2D and 3D echocardiographic measurements of the TA and leaflets with their corresponding intra-operative equivalents. Our results can be summarized as described below:

1) 3D echo and intra-operative measurements of the TA area and perimeter were similar and correlated well.
2) Two-dimensional TA diameters significantly differed between 3D echo and intra-operative measurements. These measures were also poorly correlated.
3) Systolic leaflet area were similar based on the two methods but were also poorly correlated.
4) Based on multivariate analysis, annulus area, perimeters, and tenting height but not diameters were significant predictors of the severity of pre-operative TR .

TA is a complex saddle shaped non-circular structure whose septal-anterior dimensions are usually 30% smaller than its latero-lateral dimensions. In the presence of FTR, this phenomenon becomes exaggerated with more dilatation of the anterior dimension than the septal one. Theoretically, this difference should make it difficult to identify a single diameter that accurately reflects the overall TA dilatation. To test this hypothesis, we measured TA dimensions using 2D and 3D echo results and validated these measurements against direct intra-operative sizing of the TA. Our study demonstrates for the first time that area and perimeter measurements of TA not only correlate better than diameters with *in vivo* measurements but also correlate better with the severity of FTR than 2D diameters. Similar findings, such as a poor correlation between 3D echocardiographic and intra-operative TA diameters, were recently reported by Dreyfus et al. [5] Unfortunately, these authors did not describe TA area and perimeter measurements.

Some other studies compared 2D and 3D echo measurements of the TA. Anwar et al. [6] and Volpato et al. [7] both reported that 2D echocardiographic TA measurements were significantly smaller than those measured using 3D echocardiography. These authors also demonstrated a low correlation between 2D-echo TA diameter compared to 3D-echo and MRI (r=0.5). However, none of these studies attempted to validate their measurements against an *in vivo* reference standard. They nonetheless underline the limits of the 2D methodology in assessing complex 3D objects, such as the TA. Recent valve treatment guidelines [1] recommend performing TVA in the mere presence of TA dilatation irrespective of the severity of concomitant FTR. In this context, accurate quantification of annular dimensions becomes of paramount importance because underestimation of these dimensions could lead to an increase in the risk of late FTR development, heart failure symptoms, and RV dysfunction [8], whereas overestimation could lead to an unnecessary overtreatment. The threshold that indicates tricuspid surgery (namely, septal-anterior diameter ≥ 40 mm) as recommended by the current guidelines was initially proposed by Chopra et al. [9] in 1989. Those authors studied 90 patients undergoing left heart valve surgery and observed that 88% of patients with severe TR exhibited a maximum diastolic SA diameter ≥ 38 mm or 21 mm/m^2. The present study confirms that an SA diameter ≥ 42 mm modestly predicts severe FTR with a sensitivity of 50% and a specificity of 81%, thus corroborating the cut-off value proposed by the guidelines. Our results nonetheless show that 3D echocardiographic measurements of annular area/perimeter and tenting height provide a much better prediction of FTR severity and should be therefore preferred as compared to 2D echocardiography.

4.1 Study limitations

Our paper has several limitations. First, in the absence of an analysis software dedicated to the TV, we used a vendor-independent software primarily designed for the MV. This software forced us to consider the TV as a two-commissure structure rather than a three-commissure structure; accordingly, we were obliged to fuse the anterior and posterior leaflet and to consider them a single leaflet. This process probably explains the poor correlation found between 3D echocardiographic results and *in vivo* leaflet measurements. Yet, we do not believe this fusion process affected the measurements of annular area and perimeter as demonstrated by the good correlation between 3D echo and *in vivo* measurements. Second, the *in vivo* evaluation was done on a flaccid heart while gently retracting the right atrium wall to optimize the exposure. This procedure probably explains the modest correlations found between 3D echo and i*n vivo* annular diameter measurements. Use of this procedure also probably explains the better correlation found between areas and perimeters based on the two methods. Last, the absence of intra-operative TR severity measurements could be viewed as a limitation. However, TR severity is known to be load-dependent and significantly underestimated under general anesthesia. This underestimation is the reason why pre-operative and not intra-operative echo measurements were used in our analysis.

5. Conclusion

Our work demonstrates the superiority of 3D compared to 2D echos in quantifying the degree of TA dilatation and in predicting FTR severity. Among the quantitative parameters derived from 3D echo, TA areas and perimeters were found to best correlate both with their intra-operative counterparts and baseline FTR severity. This finding suggests that 3D echo should be the preferred method for evaluating TA dilatation and eventually indicating tricuspid surgery.

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Tricuspid annular dynamics, not diameter, predicts tricuspid regurgitation after mitral valve surgery

Tricuspid annular dynamics, not diameter, predicts tricuspid regurgitation after mitral valve surgery: Results from a prospective randomized trial

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Abbreviations

FTR = Functional Tricuspid Regurgitation, TR = tricuspid Regurgitation, ACC = American College Cardiology, AHA = American Heart Association, ESC = European Society of Cardiology, TA = Tricuspid Annulus, TVP- = not Tricuspid Valve Plasty, TTE = Trans Thoracic Echocardiography, RV = Right Ventricle, TEE = Trans Esophageal Echocardiography, ES = Early Systole, MS = Mid-Systole, LS = Late Systole, ED = Early Distole, MD = Mid-Diastole, LD = Late Diastole, SA = Septal Anterior, LL = Latero Lateral, COPD = Chronic Obstructive Pulmonary Disease, NYHA = New York Heart Association, HR = Hazard Ratio, BSA = Body Surface Area, PVD = peripheral vascular disease, LVEDD = Left Ventricle End-Diastolic Diameter; LVESD = Left Ventricle End-Systolic Diameter; LVEDV = Left Ventricle End-Diastolic Volume; LVESV = Left Ventricle End Systolic Volume; EF = Ejection fraction; LV = Left Ventricle; LA = Left Atrium; RA = Right Atrium; MR = Mitral Regurgitation; VC = Vena Contracta; ERO = Effective Regurgitant Orifice; TAPSE = Tricuspid Annular Phase Systolic Excursion; RVED = Right Ventricle End Diastolic; RVES = Right Ventricle End Systolic; FAC = Fractional Area change; TR = Tricuspid Regurgitation; PAP = Pulmonary Artery Pressure; SL = Septal Leaflet; AL = Anterior Leaflet; PL = Posterior Leaflet;

Central Message

The tricuspid annulus's saddle shape and annular displacement rathen than the simple diameter or area predict post-operative functional tricuspid regurgitation.

Perspective Statement

In patients treated with mitral valve surgery, three-dimensional echocardiography-derived annular parameters predict post-operative functional tricuspid regurgitation as a surrogate of right ventricle function and thus tricuspid regurgitation derived from subclinical dysfunction of the right ventricle.

ABSTRACT

Objective: Current guidelines advise using prophylactic tricuspid valve annuloplasty (TVA) during mitral valve (MV) surgery, especially in the presence of annular diameter enlargement. However, several retrospective studies and a prospective randomized study from our department could not confirm that diameter enlargement is predictive of late regurgitation. We examined whether two- and three-dimensional echocardiographic (2D and 3D echo) and clinical characteristics could identify patients who will develop moderate or severe recurrent tricuspid regurgitation (TR).

Methods: Patients with less than severe functional tricuspid regurgitation (FTR) were randomized not to receive tricuspid annuloplasty (TA), and 11 of 53 of them were excluded from the study because 3D echo analysis was not possible. Cox regression was used to estimate the model-based probability of moderate or severe FTR (vena contracta [VC] ≥ 3 mm) or progression of TR and FTR regression using valve dimensions (annulus area, diameter perimeter, nonplanar angle, and sphericity index), dynamics (annulus contraction, annulus displacement, and displacement velocity), and clinical parameters as possible predictors.

Results: At a median follow-up of 3.8 years (range 3–5.6 years), 17 patients had moderate or severe FTR or TR progression, and 13 had FTR regression. Our models identified annular displacement velocity as a significant predictor for FTR recurrence and nonplanar angle as a significant predictor for FTR regression.

Conclusion: Annular dynamics, rather than dimension, predict FTR recurrence and regression. Annular contraction should be systematically investigated as a possible surrogate of right ventricle function to prophylactically treat the TV.

Key Words: Tricuspid valve, annuloplasty, tricuspid regurgitation

INTRODUCTION

Severe functional tricuspid regurgitation (FTR) is associated with reduced exercise capacity and decreased long-term survival[1,2]. Severe FTR seldom decreases spontaneously after left-sided valve surgery,[3] and both the American College of Cardiology/American Heart Association and European Society of Cardiology (ACC/AHA and ESC, respectively) guidelines[4] recommend performing tricuspid annuloplasty (TA) on patients with severe FTR who are undergoing left-sided valve surgery as a Class I indication. However, it remains uncertain whether patients with milder degrees of FTR should also undergo prophylactic tricuspid surgery.

The results of recent non-randomized[5] and randomized[6] studies suggest that such patients do benefit from the addition of TA to left-sided valve surgery as they display less post-operative TR,[5] improved functional capacity,[7] and better right ventricular (RV) function.[8] Accordingly, recent ACC/AHA and ESC guidelines now recommend performing TV annuloplasty as a Class IIa indication in patients undergoing left-sided valve surgery provided that they exhibit both mild to moderate TR and a dilated TA (21 mm/m^2 or 40 mm). These cutoff values were previously found to best discriminate between patients with and without severe TR after left-sided valve surgery.[9] However, recent studies have questioned the validity of these anatomical criteria as these criteria have failed to demonstrate any meaningful association between pre-operative two dimensional echocardiographic (2D echo) TA dimensions and either the presence or severity of post-operative TR.[10,11]

Because the TV has a complex 3D and non-circular geometry, 2D echo may not be the most accurate method for TA quantification[12] In this regard, we recently demonstrated that 3D echo measurements of the TA correlate better with *in vivo* surgical measurements than 2D echo measurements.[13] Based on these observations, the aim of the present study was to assess the capability of 3D echo to identify patients who will develop or exhibit persistent moderate or severe FTR after mitral valve (MV) surgery.

METHODS

Study Population

Between May 2009 and December 2010, 106 patients with less than severe FTR (< 7 mm vena contracta [VC]) were enrolled in a randomized trial to evaluate the effects of tricuspid valve annuloplasty (TVA) on the persistence or recurrence of moderate to severe post-operative FTR. Patients with primary disease of the TV were excluded. The surgical protocol and techniques were previously described, and the clinical and echo results were reported[6]. The study protocol was approved by the Institutional Review Board (Ethical committee, Cliniques Universitaires Saint-Luc, approval number: 03604484, date of approval 01/02/2009), and each patient gave written informed consent before inclusion. This study is a sub-analysis of the randomized trial. From the original population, among patients who were not treated by TVA (TVP$^-$, 53 patients), 42 had 3D echo images available and were included in the study population.

Pre- and Post-operative 2D Transthoracic Echocardiography

Standardized pre- and postoperative transthoracic echocardiography (TTE) examinations were performed according to established guidelines using iE33 Ultrasound Systems (Philips Medical Systems, Andover, MA, USA), which was equipped with a 3.5/1.75-MHz phased-array transducer. For offline analysis, images were stored on an XCELERA 2.1 PACS server (Philips Medical Systems). Four chamber views centered on the right ventricle (RV) were used to evaluate RV dimensions and function and to measure TA dimensions. Magnified 2D color Doppler images centered on the TV were used to measure the VC of the TR jet.

Intra-operative 2D and 3D Transesophageal Echocardiography

Experienced cardiologists or anesthesiologists performed all transesophageal echocardiographic (TEE) examinations after induction of general anesthesia and prior to cardiopulmonary bypass using an iE-33 ultrasound system equipped with an X7-2t TEE probe (Philips Medical Systems). First, 2D standard and magnified color Doppler images of the tricuspid valve were acquired at an average frame rate of 55 to 60 Hz. TA diameter was measured at end-systole and end-diastole from three different views: 1) a 4-chamber view, 2) RV inflow–outflow view, and 3) transgastric right ventricle inflow view. 3D echo images of the TA were then acquired during brief periods of breath holding without electrical interference or patient movement over 4 to 8 cardiac cycles. Great care was taken to include the entire TA within the 3D volume.

3D Echo Data Analysis

3D echo datasets were analyzed offline using Image Arena software (Tom-Tec Corporation GmBH, Munich, Germany) and the 4D MV analysis package. This package was initially designed for the semi-automatic identification and measurements of the mitral annulus and leaflets throughout the entire cardiac cycle. However, we recently demonstrated that it can also be used to assess the dimension and shape of the TA.[13]

For annular measurements, only six specific time-points were analyzed: 1) early systole (ES): the first frame after closure of the tricuspid valve; 2) late systole (LS): the last frame prior to tricuspid valve opening; 3) mid-systole (MS): the midpoint between ES and LS; 4) early diastole (ED): the first frame after valve opening; 5) late diastole (LD): the last frame prior to completing tricuspid valve closure; and 6) mid-diastole (MD): the midpoint between ED and LD. For each of the prespecified time points, the software automatically generates several measurements: 1) the maximal diameter from the septum to the anterior leaflet (SA diameter); 2) the lateral–lateral diameter (the largest diameter perpendicular to the previous); 3) the annulus area (2D and 3D); 4) the annulus perimeter (2D and 3D); 5) the annulus height; 6) the sphericity index of the annulus; 7) the annular displacement and displacement velocity (defined as the longitudinal movement of the annulus centroid and its first derivative); 8) the annular area fraction (defined as max annulus area − min annulus area)/(max annulus area); and 9) the nonplanar angle defined as the angle between the two vectors from the two hinge points of the annulus in the SA plane to the center of the lateral–lateral axis (Supplemental material).

Endpoints of the Study

The primary endpoint was the presence of greater than mild FTR (defined as VC ≥ 3 mm) in the latest post-operative TTE image available or an increase in FTR severity (increase in VC width of ≥ 2 mm) from the preoperative transthoracic echo to the last postoperative transthoracic echo available. The secondary endpoint was the regression of FTR, which was defined as a reduction in the VC width of ≥ 2 mm between pre- and post-operative echos. The definition of the VC threshold was derived from the intra- and inter-rater reliability analysws of the FTR. Those measurements were 0.09 ± 0.3 and 0.15 ± 0.4 mm, respectively; therefore, we chose the 2 mm threshold after considering the variability of the FTR measurements.

Statistical Analysis

All analyses were conducted with RStudio software (Version 1.0.153–© 2009–2017 RStudio, Inc.). Continuous variables were expressed as the mean ± standard deviation (SD), categorical variables were expressed as counts and percentages, and follow-up times were expressed as medians and ranges. Continuous variables were compared using a student's t- or the Mann–Whitney U-test.

Categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. Kaplan–Meier curves and Cox proportional hazard regression analyses were used to identify the factors independently associated with the primary and secondary endpoints. Penalized smoothing splines were used to show the association between independent predictors as continuous variables and the risk of primary and secondary endpoints and to identify adequate cut-off values. A sensitivity analysis were performed for the primary and secondary outcome after exclusion of the patients who underwent re-operation or died during the follow-up.

RESULTS

Clinical, Hemodynamic, and Echocardiographic Characteristics

The study population was divided into three groups: 1) Group 1 consisted of patients exhibiting at least moderate post-operative FTR or presenting with worsening FTR, 2) Group 2 consisted of patients showing TR regression, and 3) Group 3 included patients with stable FTR between pre- and post-operative echos. Table 1 shows their clinical characteristics. No significant differences were found between groups.

TABLE 1. Clinical, hemodynamic, and echocardiographic characteristics

Parameters	All	TR progression	TR regression	Stable TR
	N = 42	N = 17	N = 13	N = 12
Demographic data				
Age, y	62 ± 14	60 ± 14	60 ± 13	68 ± 15
Male, n (%)	27 (64)	10 (66)	10 (66)	7 (58)
BSA, m^2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.7 ± 0.3
Risk factor				
Arterial hypertension, n	20 (47)	8 (53)	6 (40)	6 (50)
Smoking, n (%)	7 (16)	3 (20)	3 (20)	1 (8)
Diabetes, n (%)	2 (5)	1 (7)	1 (7)	0 (0)
Comorbidities				
Stroke, n (%)	2 (5)	0 (0)	1 (7)	1 (8)
COPD, n (%)	3 (7)	0 (0)	1 (7)	2 (17)
PVD, n (%)	1 (2)	1 (7)	0 (0)	0 (0)
Kidney failure, n (%)	1 (3)	0 (0)	0 (0)	1 (8)
Sinus rhythm, n (%)	36 (85)	14 (93)	13 (87)	9 (75)
Symptoms and etiology				
NYHA III-IV, n (%)	11 (26)	4 (26)	2 (13)	5 (41)
Degenerative, n (%)	27 (64)	11 (73)	8 (53)	8 (66)
Barlow, n (%)	8 (19)	2 (13)	4 (27)	2 (17)
Rheumatic, n (%)	7 (16)	2 (13)	3 (20)	2 (16)

TR, Tricuspid regurgitation; *BSA*, body surface area; *COPD*, chronic obstructive pulmonary disease; *PVD*, peripheral vascular disease; *NYHA*, New York Heart Association.

Hemodynamic and echo characteristics of the three groups are shown in Tables 2 and 3, respectively. As shown, the three groups differed in the severity of pre-operative FTR, which was significantly lower in group 3 than in the two other groups. Group 2 had smaller nonplanar angles, and group 1 displayed lower annular displacement velocity and lower absolute annular displacement. Interestingly, no significance differences in annular dimensions were found between the three groups.

TABLE 2. Preoperative 2D echocardiographic data

Parameters	All N = 42	TR and progression TR N = 17	Regression TR N = 13	Stable N = 12
LV dimension and function				
LVEDD, mm	52 ± 10	52 ± 9	52 ± 7	53 ± 15
LVESD, mm	34 ± 8	35 ± 9	33 ± 7	32 ± 9
LVEDV, mL	228 ± 67	228 ± 59	227 ± 79	231 ± 63
LVESV, mL	91 ± 43	91 ± 43	90 ± 48	91 ± 38
EF, %	60 ± 10	61 ± 12	61 ± 9	57 ± 7
LV stroke volume, mL	40 ± 29	48 ± 26	24 ± 33	43 ± 31
Atrial dimension				
LA vol, mL	113 ± 53	126 ± 72	107 ± 45	105 ± 29
RA vol, mL	67 ± 40	66 ± 32	54 ± 27	85.3 ± 62
Mitral valve				
Pre-VC MR, cm	0.7 ± 0.3	0.8 ± 0.3	0.7 ± 0.3	0.7 ± 0.3
Pre-ERO PISA MR, cm^2	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.2
RV dimension and function				
TAPSE RV, mm	2 ± 0.6	2.1 ± 0.5	2 ± 0.4	2.2 ± 0.9
RVED area, cm^2	23 ± 5	24 ± 5	23 ± 5	24 ± 4
RVES area, cm^2	15 ± 3	15 ± 4	14 ± 3	14 ± 2
RV FAC, %	36 ± 9	35 ± 10	36 ± 9	37 ± 7
RV basal diameter, mm	42 ± 7	42 ± 7	42 ± 7	41 ± 9
RV mid-diameter, mm	36 ± 9	36 ± 6	33 ± 6	41 ± 16
PAP systolic, mm Hg	39 ± 18	39 ± 15	44 ± 16	31 ± 23
Tricuspid valve				
TR mild	20 (47%)	8 (53%)*	10 (66%)†	2 (16%)
TR moderate	7 (16%)	2 (13%)†	5 (33%)†	0 (0%)
TR vena contracta, mm	2.0 ± 2.1	1.4 ± 2.1	3.7 ± 1.4*,†	0.4 ± 1.0

2D, 2-Dimensional; *TR*, tricuspid regurgitation; *LV*, left ventricular; *LVEDD*, left ventricle end-diastolic diameter; *LVESD*, left ventricle end-systolic diameter; *LVEDV*, left ventricle end-diastolic volume; *LVESV*, left ventricle end-systolic volume; *EF*, ejection fraction; *LA*, left atrium; *RA*, right atrium; *VC*, vena contracta; *MR*, mitral regurgitation; *ERO*, effective regurgitant orifice; *TAPSE*, tricuspid annular phase systolic excursion; *RV*, right ventricle; *RVED*, right ventricle end diastolic; *RVES*, right ventricle end systolic; *FAC*, fractional area change; *PAP*, pulmonary artery pressure. *$P < .01$ versus TR and regression group. †$P < .01$ versus stable group.

TABLE 3. Preoperative 3D echocardiographic data

Parameters	All	TR and progression	Regression TR	Stable
	N = 42	N = 17	N = 13	N = 12
Annulus dimension				
SA diameter, mm	33 ± 7	33 ± 7	32 ± 6	34 ± 7
LL diameter, mm	35 ± 7	34 ± 5	36 ± 7	36 ± 8
Sphericity index	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	1.0 ± 0.1
Nonplanar angle, °	162 ± 13	165 ± 11*	153 ± 14†	169 ± 7
Circumference (3D), cm	11 ± 2	11 ± 2	11 ± 2	12 ± 2
Area (2D), cm^2	9 ± 3	9 ± 2	9 ± 3	10 ± 4
Area (3D), cm^2	10 ± 3	9 ± 3	10 ± 3	10 ± 4
Height, cm	0.7 ± 0.2	0.7 ± 0.3	0.6 ± 0.2	0.6 ± 0.2
Tenting values				
Tenting volume, mL	0.7 ± 0.8	1.2 ± 1.1	0.5 ± 0.5	0.3 ± 0.1
Tenting area, cm^2	0.6 ± 0.5	0.7 ± 0.4	0.6 ± 0.6	0.5 ± 0.4
Tenting height, mm	19 ± 16	26 ± 21	14 ± 10	18 ± 12
Leaflet dimension				
SL area, cm^2	4.1 ± 1.8	4.1 ± 1.6	4.0 ± 1.7	4.3 ± 2.3
AL + PL area, cm^2	7.7 ± 2.9	7.5 ± 2.7	7.8 ± 3.0	8.0 ± 3.1
SL length, cm	1.4 ± 0.5	1.4 ± 0.3	1.3 ± 0.4	1.5 ± 0.7
AL + PL length, cm	2.3 ± 0.9	2.2 ± 0.6	2.7 ± 1.4	2.2 ± 0.5
Annular dynamics				
Displacement, mm	9.9 ± 5.5	7.9 ± 2.7	11.3 ± 8.4	11.0 ± 3.2
Displacement velocity, mm/s	38 ± 13	31 ± 8†	38 ± 15	46 ± 11
Annulus area fraction, %	14 ± 8	12 ± 4	12 ± 5	18 ± 11

3D, 3-dimensional; *TR*, tricuspid regurgitation; *SA*, septal anterior; *LL*, laterolateral; *2D*, 2-dimensional; *SL*, septal leaflet; *AL*, anterior leaflet; *PL*, posterior leaflet.
*$P < .01$ compared with regression of TR. †$P < .01$ compared with the stable group.

Outcomes

The median follow-up was 3.1 years. During follow-up, three patients died: 1) one patient from acute pulmonary bleeding, 2) one from progressive pulmonary insufficiency (severe COPD), and 3) one from progressive heart failure. The overall 5-year survival rate was 92±4%. During the same period, three patients needed mitral re-operations because of recurrent severe MR. The overall 5-year rate of freedom from reoperation was 89% ± 6%. At the end of follow-up, 94% of the patients were in New York Heart Association (NYHA) class I-II.

Primary Endpoint

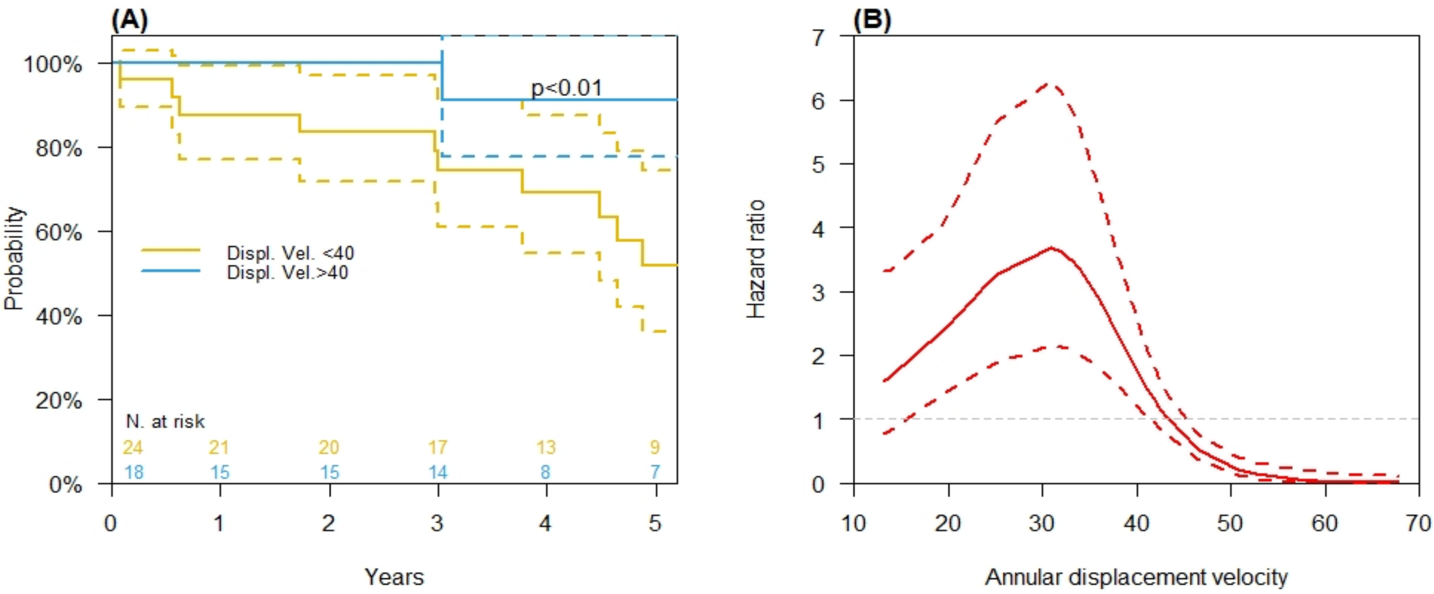
At the end of follow-up, 17 patients displayed greater than mild FTR or had experienced FTR progression. The Cox regression analysis identified LS annular displacement velocity as the sole independent predictor of persistent or progressing FTR (hazard ratio [HR] 0.93, confidence interval [CI] 0.87–0.99; p = 0.02; Table 4). Using a penalized spline function analysis (Figure 1), a cutoff value of 40 mm/s for the annular displacement velocity was found to best predict the primary endpoint with sensitivity of 94%, specificity of 50%, overall accuracy of 78%, and area under the reeiver operating characteristic (ROC) curve of 75%. As shown in Figure 3, the 5-year rate of freedom from the primary endpoint was significantly better in patients with LS annular displacement velocities of more than 40 mm/s.

TABLE 4. Cox analysis for TR or its progression

	Univariate		Multivariate	
Parameters	**HR**	***P* value**	**HR**	***P* value**
LS displacement velocity, mm/s	0.93	.02	0.93	.02
MS displacement, mm	0.75	.04		
LS tenting height, cm	1.5	.08		
Annulus area fraction, %	0.92	.13		
PAP systolic, mm Hg	1.06	.16		

TR, Tricuspid regurgitation; *HR*, hazard ratio; *LS*, late systole; *MS*, midsystole; *PAP*, pulmonary artery pressure.

FIGURE 1. A. Kaplan–Meier curve of moderate to severe functional tricuspid regurgitation (FTR) in function of annular displacement velocity with 95% confidence intervals. B. Spline function of hazard risk of FTR and its progression in function of annular displacement velocity with 95% confidence intervals.



Secondary Endpoint

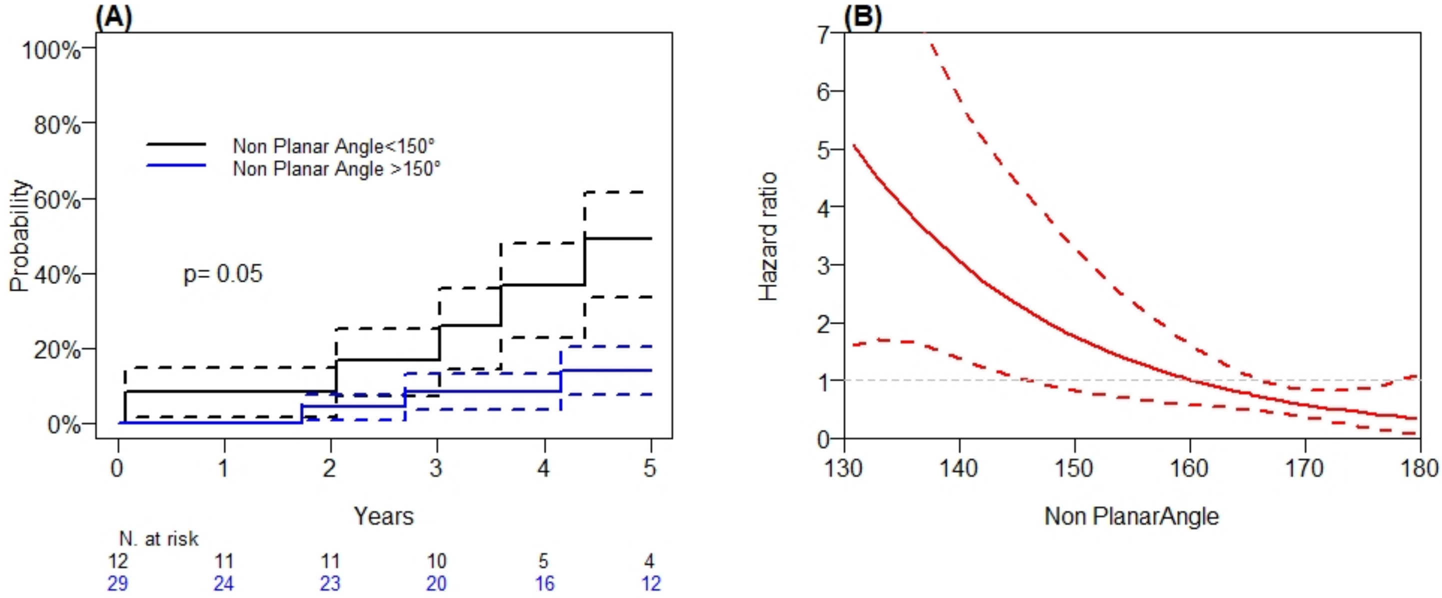
At the end of follow-up, 13 patients experienced FTR regression. The Cox regression analysis identified the MD nonplanar angle as the sole independent predictor of FTR regression (HR = 0.92, CI 0.86–0.98, p value = 0.01; Table 5). Using penalized spline function analysis, a cutoff value of 165° for the nonplanar angle was found to best predict FTR regression with sensitivity of 92%, specificity of 68%, overall accuracy of 77%, and area under the ROC curve of 75%. As shown in Figure 4, the 5-year rate of freedom from the secondary endpoint was significantly better in patients with a nonplanar angle less than 150°.

TABLE 5. Cox analysis for regression of TR

Parameters	Univariate		Multivariate	
	HR	*P* value	HR	*P* value
MD nonplanar angle	0.91	.006	0.91	.006
LS sphericity index	0.03	.05		
LS tenting height	0.65	.11		
ES annular displacement	0.77	.21		

TR, Tricuspid regurgitation; *HR*, hazard ratio; *MD*, mid-diastole; *LS*, late systole; *ES*, early systole.

FIGURE 2. A. Kaplan–Meier curve of FTR regression in function of annulus non-planar angle with 95% confidence intervals. B. Spline function of hazard risk of FTR regression in function of annulus nonplanar angle with 95% confidence intervals.



DISCUSSION

The aim of the present study was to assess the ability of 3D echocardiography to identify patients who will develop or exhibit persistent moderate or severe FTR after mitral valve surgery. Our findings can be summarized as described below:

1) Pre-operative annular dimensions, including diameter, area, and perimeter, did not differ among patients with stable, progressing, or regressing FTR after mitral valve surgery.

2) Pre-operative annular displacement velocity was lower in patients with progressing FTR than in those with stable FTR, and annular displacement velocity was the only parameter able to predict FTR progression over time.

3) The nonplanar angle was smaller in patients with regressing FTR than in those with either stable of progressing FTR and was also the only parameter able to predict FTR regression over time.

The usefulness of TVA for patients undergoing mitral surgery remains a matter of debate. Based on the observations made by Dreyfus et al.,[14] the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate performing tricuspid ring annuloplasty in the presence of mild or moderate TR and concomitant annular dilatation. Chopra et al.[9] proposed first proposed the threshold recommended by the guidelines to indicate tricuspid surgery in 1989 (namely, septal-anterior diameter ≥ 40 mm). They studied 90 patients undergoing left heart valve surgery and observed that 88% of patients with severe TR exhibited a maximum diastolic SA diameter ≥ 38 mm or 21 mm/m^2. We recently demonstrated[13] that an SA diameter ≥ 42 mm predicts severe FTR with a sensitivity of 50% and a specificity of 81%, thus corroborating the cutoff value proposed by the guidelines. In the same study, we also showed that preoperative 3D echo measurements of annular area/perimeter and tenting height provided a much better prediction of pre-operative FTR severity and could thus be the preferred method for assessing annular dilatation.

In the present study, we investigated whether the pre-operative 3D echo-derived annular area/perimeter could also predict spontaneous post-operative changes in TR severity. Surprisingly, none of the 3D annular dimensional parameters correlated with changes in post-operative TR. This finding is in line with the findings of Sordelli et al.,[16] who were also unable to demonstrate any significant correlation between 3D annular dimensions and post-operative TR severity. Nonetheless, our study identified two independent parameters associated with post-operative TR dynamics: 1) the tricuspid annular displacement velocity and 2) the annular nonplanar angle.

Annular Displacement

The annular displacement parameter that we measured is analogous to the tricuspid annular plane systolic excursion (TAPSE), a well-known index of RV function. The relationship between the RV diameter or function and FTR after TV surgery has been previously demonstrated.[17,18] In a recent series of 688 patients undergoing MV surgery and treated for FTR, Calafiore[17] reported that the major predictors of recurrent severe TR were TV apparatus remodeling and RV dilatation. Florescu et al.[19] reported similar results in patients with pulmonary hypertension.[3] In the present study, we did not observe any significant relationship between FTR and RV dimensions or volumes, which was probably due to our exclusion of patients with severe FTR. However, we did observe a significant relationship between the velocity of annular displacement and FTR progression, suggesting a possible link between subclinical RV dysfunction and the development of post-operative FTR. Further studies are needed to confirm this hypothesis.

Nonplanar Angle

The nonplanar angle is an index of the saddle shape of the TA. Our study demonstrates that the maintenance of a saddle-shaped TA is needed for FTR to regress after mitral surgery. Previous investigators have also reported similar results.[20, 21] Nonetheless, in each of these studies, development of FTR was also linked to annular dilatation. This finding was not necessarily the case in our study since only eight patients (only in the regression group) exhibited annular dilatation. This finding could indicate that TA flattening precedes the development of TA dilatation and subsequent FTR.

Taken together, these data suggest that the development of FTR after a mitral procedure, is the result of the complex interplay between the shape, dimension, and function of both the TA and the RV. Our data suggest that subclinical RV dysfunction and reduced saddle shape of the tricuspid annulus are the initial triggers and precede annular dilation and RV remodeling. Accordingly, TVA should probably be performed before the onset of annular or RV dilatation in the presence of these triggers. Nonetheless, larger studies are needed to support this approach.

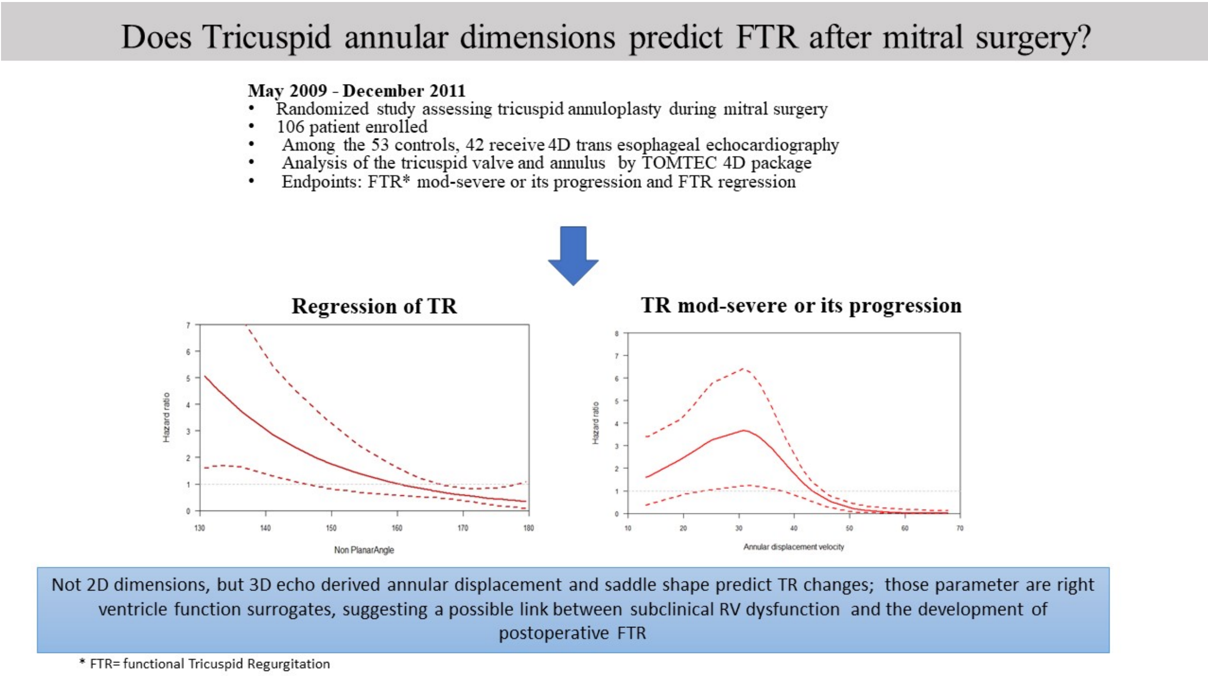
Limitations

Our study has limitations that should be acknowledged. Despite the prospective design, the analysis was retrospective and limited to patients with available 3D images. Therefore, the results need to be confirmed in larger prospective cohorts. Furthermore, we did not have specific analysis software dedicated to the tricuspid valve, so we used a vendor-independent software that was primarily designed for the MV. Use of this type of software forced us to consider the TV as a two-commissure rather than a three-commissure structure. This consideration probably affected most of the leaflet measurements and likely explains why none of these measurement stood out in the analysis. However, we do not believe that it affected the assessment of the TA dynamics as visually, TA was always well tracked by the software throughout the cardiac cycle.

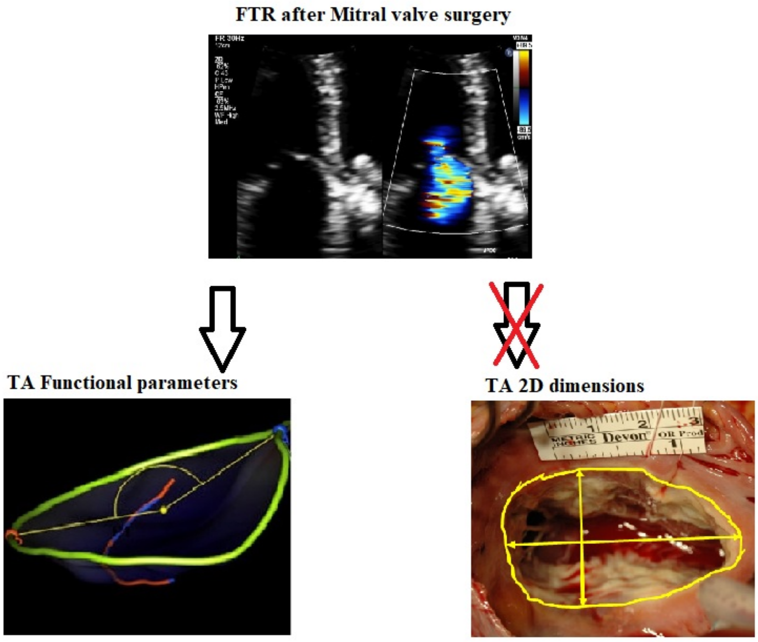
CONCLUSION

Our study identified 3D echo-derived annular displacement and saddle shape as possible early predictors of TR changes after MV surgery. Nevertheless, our findings should be considered more as hypothesis generating since additional studies are needed to clarify their role in indicating concomitant TA surgery in patients undergoing left heart-valve interventions.

Graphical abstract: Three-dimensional echocardiographic-derived annular displacement and saddle shape predict tricuspid regurgitation (TR) changes suggesting a possible link between subclinical RV dysfunction and the development of post-operative functional tricuspid regurgitation (FTR).

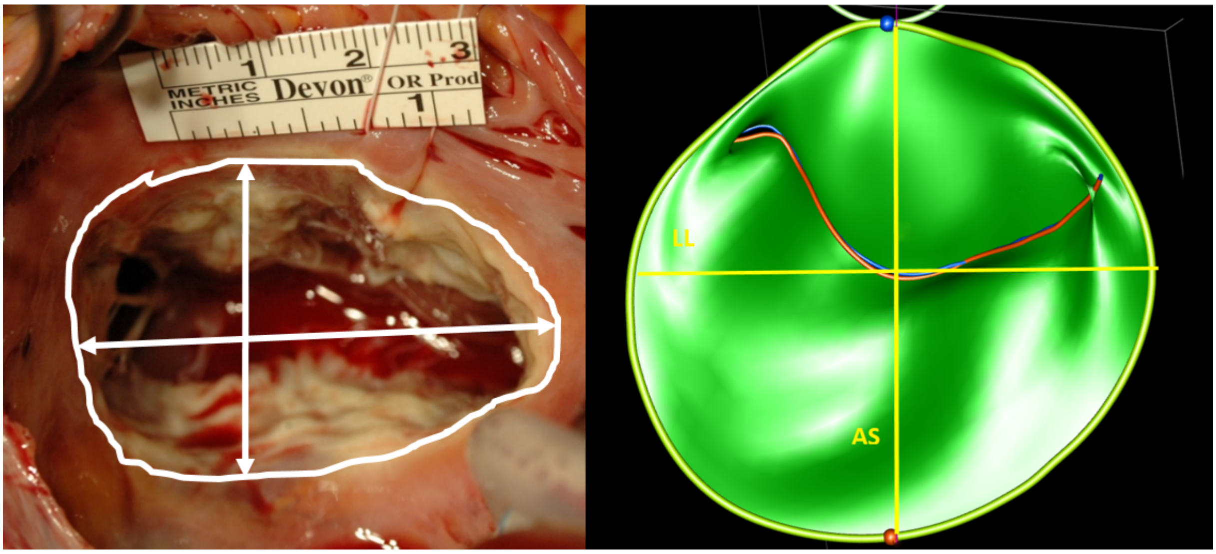


Central picture: Post-operative FTR is best predicted by functional parameter of the tricuspid annulus. FTR= Functional Tricuspid Regurgitation, TA= Tricuspid Annulus, 2D= two-dimension



Supplement material

FIGURE 5. Intra-operative picture of the tricuspid valve (left panel) with measurements used in the analysis. Right panel annular measurements obtained from the echocardiographic analysis.



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Conclusion and Perspectives

The long standing debate revolving around TV treatment at the moment of MV surgery was the core of this thesis. The use of a more aggressive approach based on annular enlargement instead of regurgitation degree has been disputed for about 15 years. The guidelines still indicate a TVA in case of TA > 40 mm or < 21 mm/m^2 based on a single centre retrospective study.

This thesis aimed to clarify several aspects of this debate. Several authors have questioned whether the use of a more aggressive and therefore frequent use of annuloplasty to reduce and repair the TA is worthwhile. To test this first hypothesis, we designed a prospective single-centre randomized study to investigate the hypothesis that concomitant TA in patients treated for left-heart valve disease prevents and improves TR progression after MV surgery and to evaluate whether this process would be associated with improved RV remodelling or a functional benefit irrespective of the annular dimension.

From the results that we obtained, we could conclude that TVA prevented recurrence of TR and the annular dimensions were not predictive of TR. However, no further effects due to TVA on clinical outcomes were noted.

Very recently, with a similar objective as found in our study, a large, multicentre randomized clinical trial was published. This trial, designed by the Cardiothoracic Surgical Trials Network, selected 401 patients who were undergoing MV surgery for degenerative MR with either moderate TR or none/trace or mild TR with TA dilatation (≥ 40 mm or index: ≥ 21mm/m^2 BSA). Those patients were randomized to receive a procedure with or without TA[1,3]. In this international randomized trial, they found that patients who underwent TA at the time of MV surgery had a significantly lower 2-year incidence of a composite endpoint of re-operation for TR, progression of TR, or death than those undergoing MV surgery alone (3.9% versus 10.2%; P = 0.02). This difference was driven by a substantially lower incidence of progression of TR among patients assigned to receive TA (0.6% versus 6.1%; p = 0.02), while the mortality (3.2% versuss 4.5%) and the re-operation rate (0% versus 0%) were similar. The incidence of moderate to severe TR was also significantly different (3.4% versus 25%). They further identified that the progression of TR occurred almost exclusively in patients with moderate TR at baseline and not in those with less-than-moderate regurgitation with annular dilatation (Table1).

<Moderate TR at Baseline[a]	**MVS Alone (N=126)**	**MVS + TA (N=124)**	**Relative Risk (95% CI)**
Primary Endpoint (Observed)	7/115 (6.1)	4/117 (3.4)	0.56 (0.17, 1.87)
Died within 2 Years	6/123 (4.9)	3/119 (2.5)	0.52 (0.13, 2.02)
TV Operation within 2 Years	0/117 (0.0)	0/116 (0.0)	-
Progression of TR at 2 Years	1/109 (0.9)	1/114 (0.9)	0.96 (0.06, 15.10)
Moderate TR at Baseline[a]	**MVS Alone (N=76)**	**MVS + TA (N=73)**	**Relative Risk (95% CI)**
Primary Endpoint (Observed)	13/72 (18.1)	3/67 (4.5)	0.25 (0.07, 0.83)
Died within 2 Years	3/75 (4.0)	3/70 (4.3)	1.07 (0.22, 5.13)
TV Operation within 2 Years	0/72 (0.0)	0/67 (0.0)	-
Progression of TR at 2 Years	10/69 (14.5)	0/64 (0.0)	-

Table 1. Post-hoc Analysis of the Primary Endpoint by Randomization Group Stratified by Moderate or less tricuspid regurgitation (TR) at Baseline

This observation gives more support in favor of the surgical indication for patients with moderate TR but on the other hand, calls into question reliance on the measurement of the TA diameter or other Echocardiographic parameter to help surgical decision making in patients with less-than-moderate

TR. This question can be answered only with additional research over a longer time period. Of note, the inclusion criteria were based on echo parameters produced by 2D echocardiography exams only. No 3D echo analyses were requested by protocol.

Similar to our findings, the author of this trial did not register any differences in clinical results. The outcomes with respect to any measures of quality of life or functional status (6-min walking test and NYHA class) as shown in Figures 1 and 2, respectively, for patients at two years were similar in the two groups. Again following these patients for a long period of time could bring more information on the clinical effect of adding a tricuspid annuloplasty, but at the moment this procedure did not add any clinical benefit.

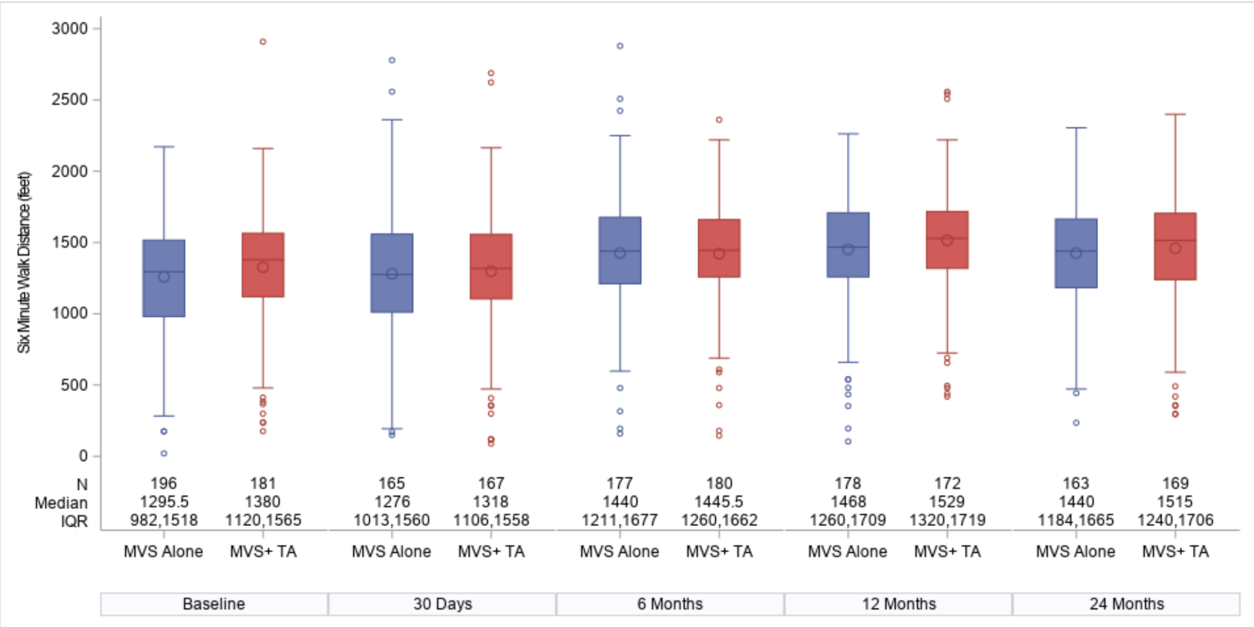

Figure 1. Six-min walking distance overtime.

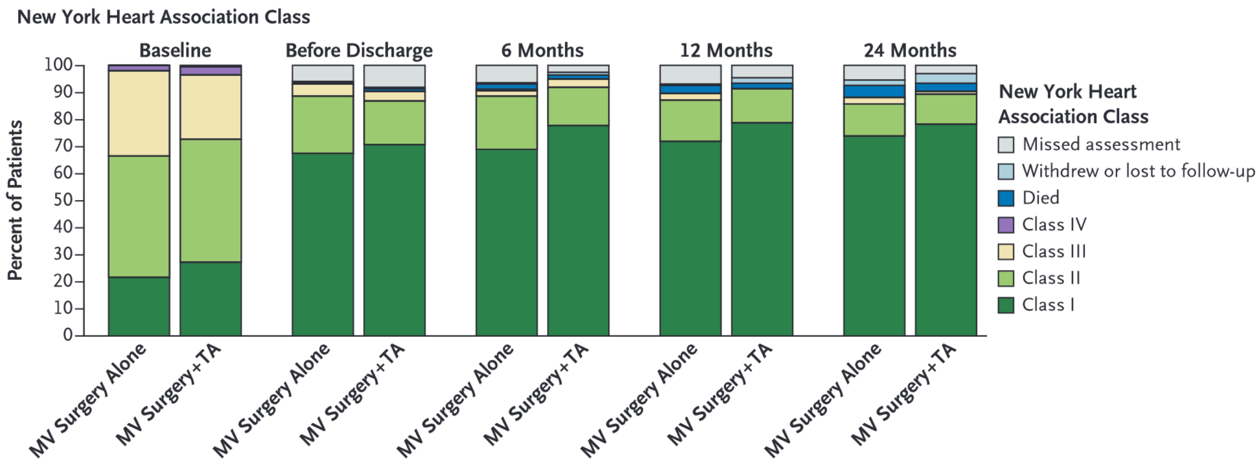

Figure 2. Six-min walking distance overtime. New York Heart Association (NYHA) class (Panel C) among the patients who were undergoing mitral valve (MV) surgery alone or MV surgery plus tricuspid annuoplasty (TA) during the two years after randomization.

An important finding in this trial was the higher incidence of permanent pacemaker implantation in the TA group (14.1% versus 2.5%) with nearly 80% of procedures occurring during the index hospitalization. Essentially, concomitant TA during mitral surgery in 20 patients prevented severe TR in about one patient and at the price of permanent pacemaker implantation in approximately two patients over two years[2]. This pacemaker rate was higher than most of other retrospective studies and also more than our randomized trial where we reported a permanent pacemaker need of 7.5% in the group of MV repair and TA. In a post-hoc analysis, the authors identify only older age and left ventricular ejection fraction (LVEF) as predictor for the need of permanent PM. In a recent meta-analysis the reported rate of permanent pacemaker was 12%, confirming this complication as the Achille's heel of this procedure. More detail analysis about preoperative echo predictors could clarify with patients have higher risk of PM implantation and who should be eventually excluded. The use of alternative technique as mitral partial ring could also be investigated, because avoiding the placement of the sutures at the level of the anterior annulus could reduce the risk of damage of the bundle of His, especially when a second ring is placed also on the tricuspid annulus.

This study represents the highest level of evidence until now concerning this topic as the data were generated by a multi-centre prospective randomized trial. Based on these results, one might conclude that current guidelines, i.e. "Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus (>_40 mm or >21 mm/m2 by 2D echo) undergoing left-sided valve surgery", are appropriate and even that the level of evidence should be raised from Level of Evidence B to a Level of Evidence A (Data derived from multiple randomized clinical trials or meta-analyses). However it should be emphasized that the results of the trial only concerned a soft endpoint, i.e. progression of echocardiographic TR, and that no clinical nor prognostic benefits were evidenced. Although this remains hypothetical, this could be in part be explained by an increased risk of permanent pacemaker in patients who underwent TA at the time of MV surgery. Specific new risk analysis are needed to identify patients at higher risk of needing a pacemaker; thus, this complication should be brought into the equation when a surgical indication is formed.

Furthermore, althoug this data indicated that patients with mild to moderate TR, TVA prevents further progression of the disease, the results of Gammie's randomized trial failed to demonstrated this was related to tricuspid annulus dilatation. Our data also demonstrated that TVA prevents tricuspid regurgitation progression, we could not find any evidence linking this progression to TA dilatation. On the contrary our results suggest that sub-clinical RV dysfunction is responsible for postoperative TR deterioration (vide infra).

The second part of the thesis question asks what is the correct parameter to quantify tricuspid annular enlargement and predict TR. To test this hypothesis, we collected the 2D and 3D echocardiographic characteristics and measurements of the TV and annulus measured intra-operatively after which we correlated those with TR during the pre-operative period in the second manuscript and during follow.-up in the last manuscript.

Our work demonstrates the superiority of 3D compared to 2D echo in quantifying the degree of TA dilatation and in predicting the severity of FTR. Among the quantitative parameters derived from the 3D echo TA area and perimeter were found to best correlate both with their intra-operative counterparts and baseline FTR severity. This finding suggests that 3D echo should be the preferred method to evaluate TA dilatation and eventually indicate tricuspid surgery.

The use of 3D echo for the evaluation of the TV is very limited, and 2D imaging remains the standard of care. Our findings demonstrate the limitation of the 2D echo; therefore, clinicians involved in the assessment and treatment of this valve should be aware of those limitations. Therefore a more systematic use of 3D imaging should be adopted in every echo lab and intra-operatively to guide correctly guide diagnosis and treatment. The current ESC/EACTS guidelines underline the importance of 3D echo only in case of RV volume determinations and in the determination of 3D VC in case of inconsistent findings during TR grading. Therefore, in lieu of the our findings, we advocate more strict recommendations in the use of 3D echo in the evaluation of the TV to quantify and analyse its anatomy because of the limitations of the 2D analysis.

In the last part of the thesis we identified new predictors for FTR progression or regression after MV surgery. For this purpose, the intra-operative 2D and 3D echo analyses were used to correlate and identify new parameters of changes in FTR at follow-up.

Our study identified 3D echo-derived annular displacement and saddle shape as possible early predictors of TR changes after MV surgery. Our data suggest that subclinical RV dysfunction and reduced saddle shape of the tricuspid annulus are the initial triggers and precede annular dilation and RV remodeling. Accordingly, TA should probably be performed before the onset of annular or RV dilatation in the presence of these triggers.

The initial idea of Dreyfus to use tricuspid annular enlargement as indicator for annuloplasty was because this parameter could precede RV dilatation/dysfunction. Therefore, the early treatment of the TV could prevent the development of FTR and RV dysfunction. Our results therefore confirm a part of this hypothesis because we identified two parameters, namely, surrogate of the RV function that could be used to identify pre-clinical RV dysfunction as predictor of FTR evolution. Therefore, the role of the RV is fundamental in this pathology. These novels parameters need to be validated by other studies and because of the complexity to obtain them, the annular displacement value need a long post-hoc analysis; therefore, new more simple and fast predictors should be investigated.

Recently, new RV parameters have been analysed in patients with FTR. One of the most used is speckle-tracking echocardiography (STE) RV free wall longitudinal strain. In a cohort of patients with significant FTR, Prihadi et al.[2] evaluated the prevalence and prognostic value of impaired RV free wall longitudinal strain, in comparison with TAPSE and fractional area change (FAC). RV free wall longitudinal strain was identified as contributing the highest percentage of all parameters to RV dysfunction (84.9%) in comparison to FAC (48.5%) and TAPSE (71.7%) as shown in Figure 1. The capability of refine the diagnosis of RV failure using this parameter could therefore improve the detection of patients with a subclinical RV dysfunction. As we demonstrated the primary risk factor to develop TR at follow-upis subclinical RV dysfunction. The use of STE techniques could improve the detection of this condition and identify who should undergo a tricuspid annuloplasty.

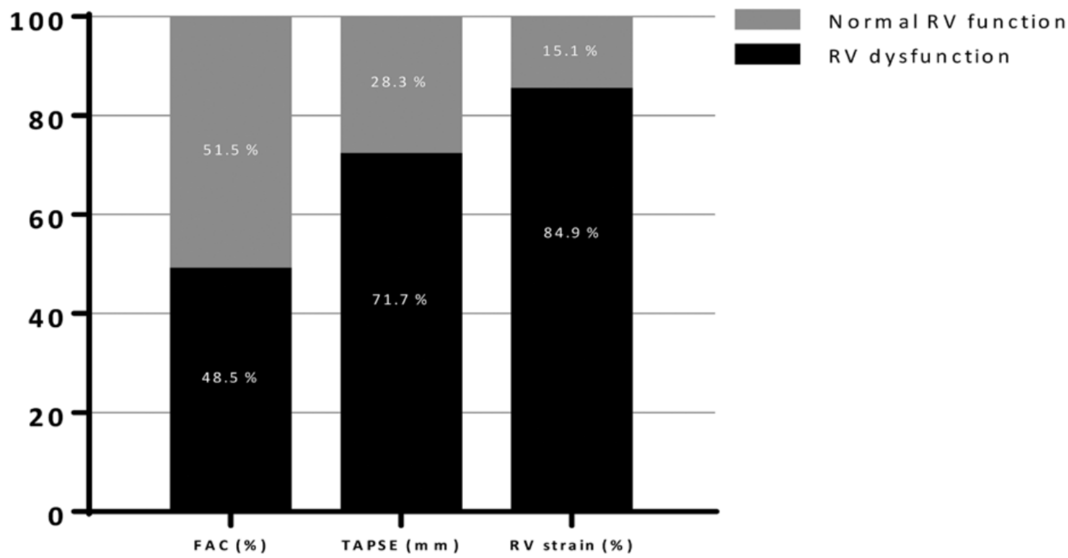

Figure 1. Distribution of right ventricular (RV) dysfunction according to different measures of RV function. Using the prespecified cut-offs for RV dysfunction (RV fractional area change [FAC] <35%, tricuspid annular plane systolic excursion (TAPSE] < 17 mm and[free wall longitudinal strain > −23%), the distribution for RV dysfunction and normal RV function are shown for the overall population.

Further when compared with survivors, non-survivors showed worse RV systolic dysfunction (RV free wall longitudinal strain = −15.9% ± 7.5% versus −12.9% ± 6.8%; $P < 0.001$). Cumulative event-free survival was significantly worse in patients with decreased FAC, decreased TAPSE, and impaired RV free wall longitudinal strain. Based on a multivariate analysis, RV free wall longitudinal strain was independently associated with all-cause mortality and incremental to FAC and TAPSE. Therefore, this parameter is a very promising predictor of RV dysfunction in cases of FTR. The use of RV strain analysis in patients undergoing surgical treatment of the MV remains limited. No large series are present at present in the literature about the correlation of RV longitudinal strain and clinical and clinical and echocardiographycal outcomes after surgical MV repair.

Another recent parameter of RV function is RV–pulmonary artery coupling. Quantification of RV–pulmonary arterial (PA) coupling, the ratio of RV function based on pulmonary artery pressure may provide important insights into the mechanism of adaptation of RV contractility to afterload in patients with secondary TR. The ratio between RV end-systolic elastance (Ees) and pulmonary arterial elastance (Ea) estimated from invasive pressure–volume loops is the reference standard. Recently, the ratio between TAPSE and pulmonary artery systolic pressure (PASP) measured using echo has shown a good correlation with invasively estimated RV–PA coupling. A reduced TAPSE/PASP ratio suggests that RV contractility is uncoupled from its load and presents poor prognosis in patients with pulmonary hypertension. In a recent paper by Fortuni et al.[3], in a group of 1149 patients with moderate to severe FTR, TAPSE/ PASP was estimated using the ratio between two standard echo measurements: 1) tricuspid annular plane systolic excursion (TAPSE) and 2) pulmonary artery systolic pressure (PASP). A total of 470 patients (41%) demonstrated TAPSE/PASP <0.31 mm/mm Hg as shown in Figure 2. Patients with rediced TAPSE/PASP presented more frequently with heart failure symptoms, had larger RV and left ventricular dimensions, and more severe TR compared to those with normal TAPSE/PASP. After correcting for potential confounders, TAPSE/PASP was the only echocardiographic parameter independently associated with all-cause mortality (hazard ratio [HR] 1.462; 95% confidence interval [CI] 1.192–1.793; $p < 0.001$). In conclusion, TAPSE/PASP in patients with secondary TR is independently associated with poor prognosis and may improve risk stratification.

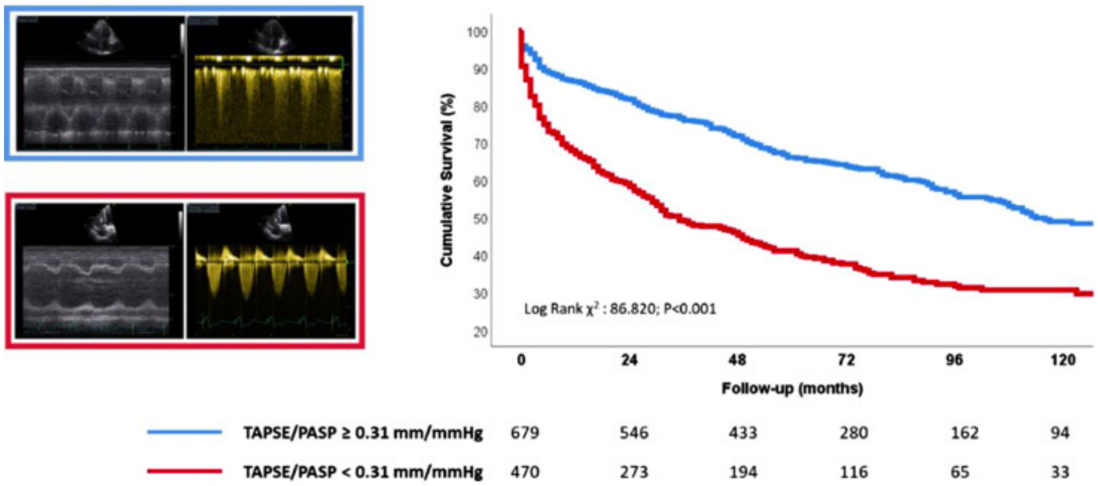

Figure 2. Kaplan–Meier curves for all-cause mortality. The Kaplan–Meier curves demonstrate the higher survival rates of patients with RV–PA coupling (TAPSE/ pulmonary artery systolic pressure [PASP] ratio: ≥ 0.31 mm/mm Hg, blue line and box) compared to those with TAPSE/PASP ratio <0.31 mm/mm Hg (red line and box) during the follow-up after significant secondary TR diagnosis.

Althoug apparently interesting, these results were nontheless anticipated. Indeed, we do TAPSE over PASP ratio would result in either a increase in PASP, reduction in TAPSE or a combination thereof, all of which are individually known to negatively affect outcomes. This is substantiated by the fact that patients with the best outcome and the highest TAPSE/PASP ratio were the ones with the best RV function and the lowest pulmonary pressure. It is therefore uncertain wheter this more complex parameters could be superior to single RV strain measurements.

In this regard, our center is performing a retrospective analysis in a large group of patients after MV repair for degenerative disease. Among 361 patients who underwent surgery between 2011 and 2017, we collected the pre-operative and all available post-operative TTE results. We performed a longitudinal analysis of right atrium, RV , left atrium and LV strain. The primary outcome of interest is the influence of the RV strain in the development of FTR. Furthermore, we will explore the changes of RV strain and RV function longitudinally. The pre-operative RV–PA coupling will be also added to the analysis. For this parameter. the RV function will be evaluated based on the RV strain instead of the FAC because of the better discrimination power of the latter. Furthermore, because the limitation of the PA pressure estimation based on echo in cases of severe TR (because of the rapid pressure equalization between RA and RV), we will consider other PA parameters, such as the diastolic PAP derived from the pulmonary regurgitation trace and the mean PAP derived from the acceleration time as measured by pulsed Doppler of the pulmonary artery in systole. We expect to have the data ready for publication around the end of 2023. This analysis could yield more information concerning the role of RV function and RV–PA coupling in FTR development or changes in addition to the evolution of RV function and RV–PA coupling after MV surgery.

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3. Fortuni, F. et al. Right Ventricular–Pulmonary Arterial Coupling in Secondary Tricuspid Regurgitation. The American Journal of Cardiology 148, 138–145 (2021).

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