REVIEW

Atrial functional tricuspid regurgitation: a novel and underappreciated clinical entity

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Abstract: Functional or secondary tricuspid regurgitation (FTR) is a progressive disease with a significant negative impact on patient morbidity and mortality. Recently, atrial fibrillation (AF) has been recognized as a cause of FTR (with/without coexisting functional mitral regurgitation) by promoting right atrial (RA) remodeling and secondary tricuspid valve (TV) annulus dilation, even in the absence of right ventricular (RV) dilation or dysfunction. This distinct form of FTR has been called "atriogenic" or "atrial". Recent evidence suggests that the RA is an important player in FTR pathophysiology not only for patients with AF, but also for those in sinus rhythm. Preliminary reports on atrial FTR show that cardioversion with documented maintenance of sinus rhythm promotes TV annulus and RA reverse remodeling and may significantly reduce FTR severity at follow-up. Large-scale studies on the prognostic benefits of rhythm vs rate-control strategy in atrial FTR patients are needed to substantiate specific guidelines indications for this subset of patients.
Keywords: atrial functional tricuspid regurgitation; tricuspid valve; three-dimensional echocardiography; transthoracic echocardiography.

Rezumat: Insuficiența tricuspidiană funcțională sau secundară (ITF) este o patologie progresivă și cu impact negativ asupra morbidității și mortalității pacienților. Recent, fibrilația atrială (FA) a fost recunoscută ca și cauză a ITF (cu/fără insuficiență mitrală funcțională asociată), prin efectele sale asupra remodelării atriului drept (AD) și dilatării secundare a inelului tricuspidian, chiar în absența dilatării sau disfuncției ventriculare drepte (VD). Această entitate particulară a ITF a fost denumită „atriogenică" sau „atrială". Dovezi recente sugerează rolul important al AD in fiziopatologia ITF la pacienții în FA, dar și la cei în ritm sinusal. Date preliminare despre ITF arată că restabilirea și menținerea ritmului sinusal după cardioversie promovează revers-remodelarea inelului valvei tricuspide și a AD, contribuind la o reducere semnificativă a severității ITF la follow-up. Studii pe scală largă despre beneficiile prognostice ale strategiei de control al ritmului vs control al frecvenței la pacienții cu ITF atrială sunt necesare pentru a susține elaborarea unor indicații de ghid specifice pentru acest subgrup de pacienți.
Cuvinte cheie: insuficiență tricuspidiană funcțională atrială; valva tricuspidă; ecocardiografie tridimensională; ecocardiografie transtoracică.

Functional or secondary tricuspid regurgitation (FTR) is a progressive disease with a significant negative impact on patient morbidity and mortality. In FTR, the retrograde flow from the right ventricle (RV) to the right atrium (RA) during ventricular systole typically occurs in the presence of structurally normal leaflets of the tricuspid valve (TV). The mechanisms of FTR are either the dilation of TV annulus, the tethering of TV leaflets, or a combination of both[1].

For years, the general belief has been that FTR is the hallmark of the disease of the RV, rather than the disease of the TV itself. According to current ESC/EACTS guidelines[2], FTR develops as a result of the geometric changes of TV apparatus due to the dysfunction of the RV following pressure and/or volume overload. Nevertheless, there are often patients with significant FTR that may present with TV annulus dilation, despite a normal RV, and a dilated RA[3]. Recently, atrial

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fibrillation (AF) has been recognized as a cause of FTR (with/without coexisting functional mitral regurgitation) by promoting RA remodeling and secondary TV annulus dilation, even in the absence of RV dilation or dysfunction (type I of the Carpentier classification)[4]. This distinct form of FTR has been called "atriogenic" or "atrial", and thanks to the use of three-dimensional echocardiography (3DE), its peculiar pathophysiologic mechanisms have now been described[5–8].

However, both the 2017 ESC/EACTS Guidelines on the management of valvular heart disease[2] and the recent 2020 ESC Guidelines on the diagnosis and management of AF[9] do not even mention this distinct form of FTR that may typically affect patients with persistent AF. Current literature addressing atrial regurgitation of the TV or mitral valve (MV) has been calling it "neglected", "an underappreciated cause", "new entity", "newly described disorder"[7,10–12]. Only recently, in the newly published 2020 ACC/AHA Guidelines for the management of patients with valvular heart disease, has the atrial mechanism of FTR been given a distinct role[13]. Yet, as there is almost no evidence available on how to manage these patients, there are more open questions than answers. Atrial FTR may require different clinical management and the various interventional treatment options may have different outcomes than in the classical ventricular FTR due to RV dilatation and dysfunction (type IIIb of the Carpentier classification)[14,15]. Since AF is the most common sustained arrhythmia (affecting ~33 million people worldwide) with an increasing prevalence due to the ageing of the population[16], clinicians and echocardiographers will likely encounter patients affected by atrial FTR.

Therefore, we aimed to familiarize the reader with this "new" disease by providing an overview of the pathophysiology, and the key distinguishing features of atrial FTR that may help the clinicians and imaging specialists to differentiate it from the classical ventricular form of FTR.

ANATOMY AND PATHOPHYSIOLOGY

The TV apparatus consists of several components – valve leaflets, annulus, chordae tendineae, papillary muscles, and RV and RA walls. Compared to the MV complex, TV has greater anatomical variability, a more apically insertion of the septal leaflet, and chordal attachments directly inserted to the interventricular septum[17]. The normal TV annulus is an elliptical, saddle-shaped, and dynamic structure. In comparison to the mitral annulus, the TV annulus is larger (normal TV diameter in apical four-chamber view 19 ± 2 mm/m^2, and 3D area 7.6 ± 1.7 cm^2/m^2), and more dynamic (systolic fractional shortening of 25% and area change of 30-40%)[18,19]. The TV annulus is mostly a fatty structure, and its significantly smaller fibrotic component with respect to the MV annulus could explain why the TV annulus dilates more easily along with the right heart chamber enlargement and is the main mechanism responsible for the development of atrial FTR[20,21]. TV papillary muscles send chordae to ipsilateral leaflet(s) and become more separated and apically displaced in the context of RV dysfunction, leading to TV leaflet tethering[1].

The classical (ventricular) form of FTR may occur in various cardiac conditions (left-sided valvular, myocardial, or pulmonary diseases) and includes three main mechanisms: 1) TV annulus dilatation due to RV remodeling; 2) changes in the geometry and dynamics of the annulus, becoming rounder, flatter and less contractile; 3) leaflet tethering as a consequence of the spatial displacement of the components of the TV apparatus resulting in loss of coaptation and secondary FTR[5,22]. Among these mechanisms, TV leaflet tethering is the primary pathophysiological mechanism of ventricular FTR. It occurs with changes in RV geometry and function due to volume and/or pressure overload, such as an increase in RV volume, RV global or regional systolic dysfunction or shape abnormalities (increased sphericity, abnormal regional curvature, etc.)[3,23]. Annular dilatation is an important contributor to the development of ventricular FTR, leading to edge-to-edge leaflet coaptation[20].

The importance of the RA has been ignored, despite the close anatomic relationship of the RA vestibule with the TV annulus. The RA vestibule is a smooth muscular rim that anchors the pectinate muscles and surrounds the TV orifice, with its thin musculature fibers inserting into the leaflet hinges[3]. In contrast with the MV annulus, which is disconnected from the left atrial myocardium between both fibrous trigones at the base of the anterior leaflet, the TV annulus has a single right fibrous trigone keeping it in closer contact with RA myocardium over a larger part of its circumference. The muscular fibers of the RA vestibule are responsible for the "sphincteric-like" contraction of TA[24], and might explain the TV annular dysfunction in AF patients with RA remodeling and atrial FTR.

The proposed model of atriogenic regurgitation - typically with long-standing persistent AF - implies a significantly remodeled RA that promotes a mar-

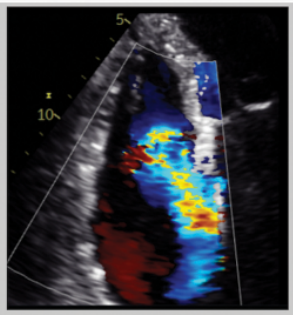
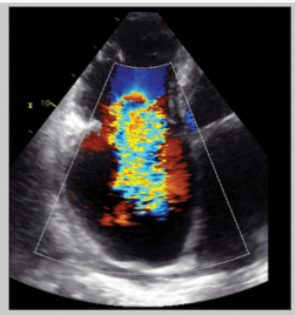
	ATRIAL FUNCTIONAL TRICUSPID REGURGITATION	VENTRICULAR FUNCTIONAL TRICUSPID REGURGITATION
		
CARPENTIER CLASSIFICATION	TYPE I	TYPE IIIb
LEAFLET MOTION	NORMAL	RESTRICTED LEAFLET CLOSURE
LEAFLET TETHERING	ABSENT/MILD	SEVERE
ANNULUS SIZE	SEVERE DILATION	NORMAL/MILD DILATION
VENTRICULAR SIZE	NORMAL/MILD DILATION	SEVERE DILATION
VENTRICULAR FUNCTION	NORMAL	REDUCED
ATRIAL SIZE	SEVERE DILATION	MILD DILATION
ATRIAL FUNCTION	SEVERELY REDUCED	MODERATELY REDUCED

Figure 1. Comparison between atrial and ventricular functional tricuspid regurgitation; adapted from 5.

ked and progressive dilatation of TV annulus in the presence of no or minimal dilation of the RV[4,25]. TV annulus is considerably enlarged in AF patients, even with less than severe FTR, and independently of the presence of cardiac structural abnormalities, supporting that TA dilation is the direct consequence of AF itself, rather than the result of FTR[26]. Compared with ventricular FTR patients and for similar FTR severity, patients with atrial FTR had increased dimensions and posterior displacement of the TV annulus, larger RA, and smaller RV[6]. Moreover, in patients with so-called "idiopathic FTR" (most of them being actually atrial FTR due to AF), Topilsky[27] observed that the RV assumes a triangular shape with dilation occurring at the basal level, resulting in a large TV annular area without leaflet tethering (Figure 1). In contrast, in patients with pulmonary hypertension and ventricular FTR, the RV becomes elliptical due to dilation occurring at the mid-ventricular level, resulting in significant valvular tethering with no or mild TV annular dilatation (Figure 2). Thus, the tethering of TV leaflets is commonly seen in patients with a ventricular form of FTR (with/without significant annular dilation) due to pressure/volume RV overload, while in atrial FTR due to AF the tethering is characteristically absent because the RV is normal. Once the pathophysiological cascade is initiated (either by ventricular or atrial factors), a vicious cycle ensues, with progressive FTR and further dilatation of the TA due to either RA or RV volume overload, resulting in further FTR and ultimately a combination of both atrial and ventricular FTR[4,28,29]. Therefore, in advanced stages with massive or torrential FTR, marked remodeling of TV apparatus, and secondary RA and RV dysfunction due to longstanding volume overload, it may be more challenging to distinguish the primary cause of FTR[6,16]. However, the prognosis of

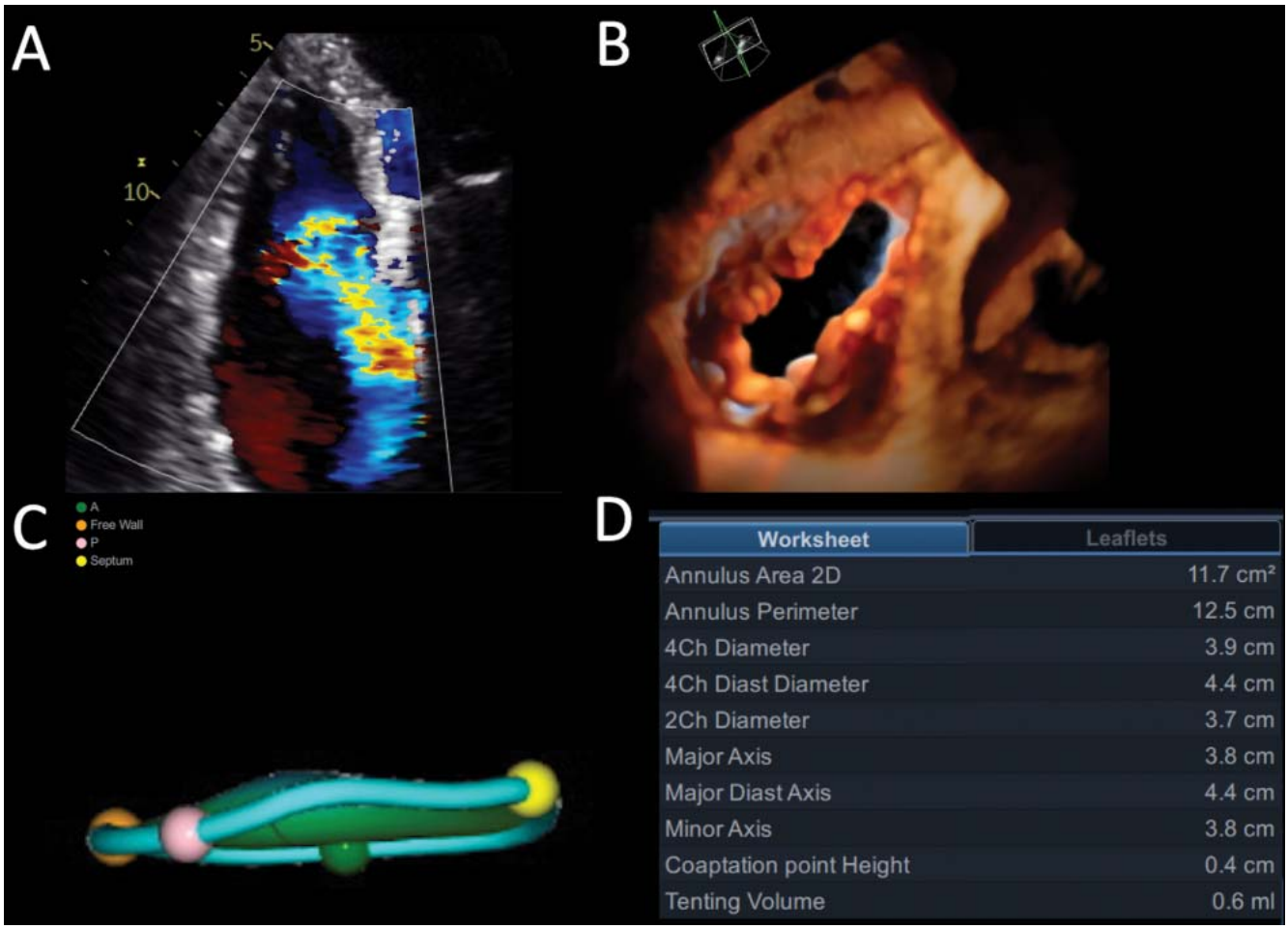


Figure 2. Atrial functional tricuspid regurgitation: RV-focused apical four-chamber color flow of the regurgitant jet (A); En face view of the tricuspid valve by 3D echocardiography (B); Tricuspid annulus geometry (C) and measurements (D) by 4D Auto TVQ software (GE Healthcare, Horten, N).

massive/torrential FTR is severe[30,31] and there is likely little clinical benefit in clarifying the pathophysiological sequence at this advanced stage of the disease. Figure 3 presents the main imaging features that may help in differentiating the atrial FTR from the ventricular FTR.

Recent evidence suggests that the RA is important not only in AF patients but also in sinus rhythm. Indeed, RA could be a major player in the development of FTR and a key determinant of TV annular dilation[32], irrespective of its cause[3]. We demonstrated that in all FTR groups (including atrial form due to AF and ventricular form due to both RV pressure and volume overload), as well as in healthy subjects, the TA area was more closely related to RA volume than to RV end-diastolic volume measured by 3DE[3].

ECHOCARDIOGRAPHIC ASSESSMENT

Transthoracic 2D-Doppler echocardiography is the primary imaging modality in the evaluation of FTR patients. By assessing TV morphology and annulus size, right-heart chambers' size and hemodynamics, echocardiography generally provides the data needed to be integrated for evaluating the mechanisms and the severity of TR and to orient the subsequent clinical management[22]. If unclear or conflicting results from transthoracic echocardiography, transesophageal echocardiography, cardiac magnetic resonance and cardiac computed tomography can be used for a comprehensive imaging assessment of the patient with FTR[33].

TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHY

The state-of-the-art echocardiographic evaluation of TR should follow several steps: 1) attesting the presence of pathological FTR; 2) evaluating the morphological characteristics of the TV; 3) assessing the key features of FTR (annulus dilation, leaflet coaptation, etc.); 4) discriminating between a ventricular and an atrial form of FTR; 5) quantifying the severity of FTR

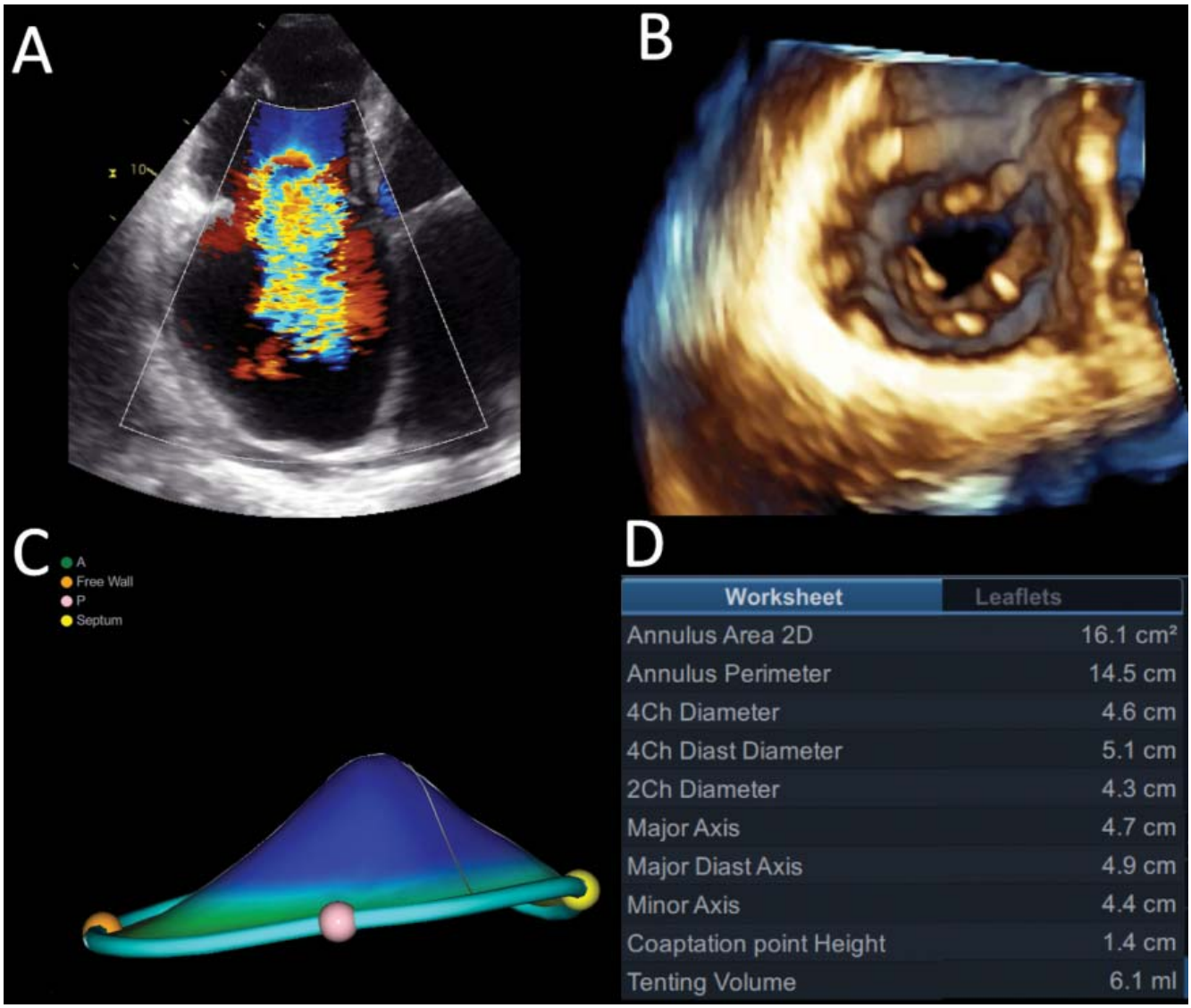


Figure 3. Ventricular functional tricuspid regurgitation in a patient with pulmonary hypertension. RV-focused apical four-chamber color flow of the regurgitant jet (A); En face view of the tricuspid valve by three-dimensional echocardiography (B); Tricuspid annulus geometry (C) and measurements (D) by 4D Auto TVQ software (GE Healthcare, Horten, N). Note the significant leaflet tethering (coaptation point height, tenting volume) with respect to Figure 2.

and its hemodynamic impact on right-heart chambers[15].

In clinical routine practice, TR assessment is performed by 2D and Doppler echocardiography as recommended by guidelines[17,34]. When quantifying TR severity, different parameters (qualitative, semi-quantitative, or quantitative) should be evaluated (Figure 4). Structural parameters include TV morphology, IVC diameter, and RV and RA size[35]. In some cases, 2D speckle-tracking echocardiography can detect the initial RV subclinical dysfunction. In advanced stages, RV dilatation is present, mainly due to chronic volume overload[22]. Qualitative parameters consist of interventricular septal motion and Doppler ones such as regurgitant color flow and continuous wave jets and flow convergence zone's characteristics (size and duration)[35,36]. A small and brief color flow jet is considered to be specific for mild regurgitation. However, grading of FTR severity based on this sole parameter is not recommended[17,34,36]. The semi-quantitative parameters comprise regurgitant jet's color flow area, PISA radius, vena contracta width, hepatic vein flow, and tricuspid inflow patterns[35]. Quantitative parameters are PISA-derived EROA and regurgitant volume. Although the majority of Doppler methods used in grading left-sided valvular heart disease are applicable

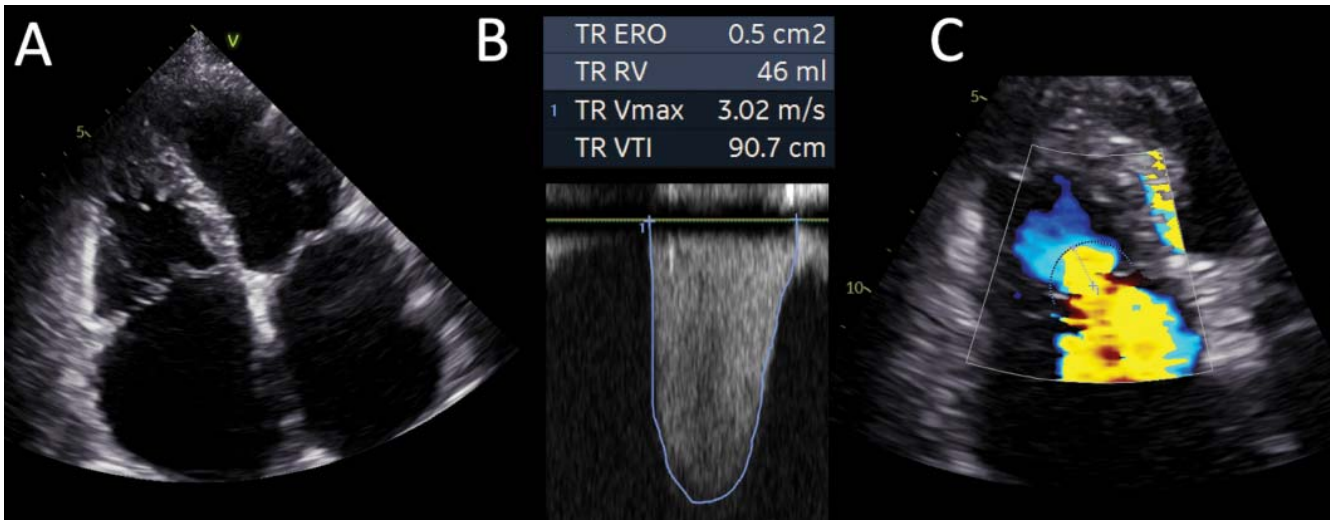


Figure 4. Atrial functional tricuspid regurgitation and quantification of its severity: RV-focused apical four-chamber view showing dilated right atrium and tricuspid annulus, with relatively preserved right ventricular size and no leaflet tethering (A); Velocity time integral (TR VTI) of tricuspid regurgitation CW Doppler jet (B) and 2D PISA radius measurement (C) allowing to calculate the effective regurgitant orifice area (TR ERO) and regurgitant volume (TR RV).

when evaluating FTR, it is important to remember that, in most cases, TR jet has lower pressure and velocity (strictly correlated to jet momentum) compared to MR. This has a direct impact on volumetric and jet analysis[35]. In addition, the current criteria for FTR severity grading are seldom used in clinical practice due to paucity of validation studies and lack of prognostic data. Recently, newly validated prognostic cut-offs for grading FTR have been proposed by our group[37]. By using patients' outcome data as reference, we found that the threshold values to define severe TR were >6 mm, >0.30 cm^2, >30 mL, and >45% for vena contracta average, EROA, regurgitant volume and regurgitant fraction, respectively. Notably, these cut-off values are significantly smaller than those recommended by current guidelines.

Even though FTR severity grading remains a challenging task, there have been formulated several specific severity indices (severe valve lesions such as flail leaflet, large, holosystolic flow convergence zone, and systolic flow reversal in the hepatic veins)[35,36].

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

When quantifying the right-chambers' sizes by 2D echocardiography (2DE), significant underestimation may occur due to foreshortening or geometrical assumptions. The 3D-derived methods allow a more accurate and reliable measure of both the RV and the RA, which is one of the key prerequisites in differentiating atrial FTR from ventricular FTR[38–40]. 3DE allows the simultaneous visualization of all three valve leaflets to reliably exclude any structural abnormalities and the quantitative automated analysis of all components of the TV apparatus accounting for their complex three-dimensional shape.

An important benefit of 3DE is increased accuracy in sizing the TV annulus.

Currently, the indication for TV annulus repair in the context of left-sided valvular disease surgery is based on a cut-off value of >40mm or >21mm/m^2 measured from the apical four-chamber view by 2DE, assuming that the annulus is symmetrical, flat, and circular[22]. Due to the complex, three-dimensional configuration, with variable spatial orientation, of the tricuspid annulus, 3DE should be the first-line modality in imaging the patient with FTR. Another key parameter to evaluate is the tethering of TV leaflets. The coaptation of TV normally occurs at the leaflets' body, at the annulus level, or just below it. With tethering of the valves, the coaptation takes place on the leaflets' free edges with consequent FTR (Figure 5). The measurements of the tethering distance and tenting area by 2DE assume a symmetrical tethering pattern and that the longest distance to the coaptation point of the three leaflets occurs exactly in the 4-chamber view plane (i.e. displaying two out of three leaflets), which is unlikely in patients with FTR. Tenting volume measured by 3DE is a more precise parameter in grading FTR severity, as it does not depend on any plane posi-

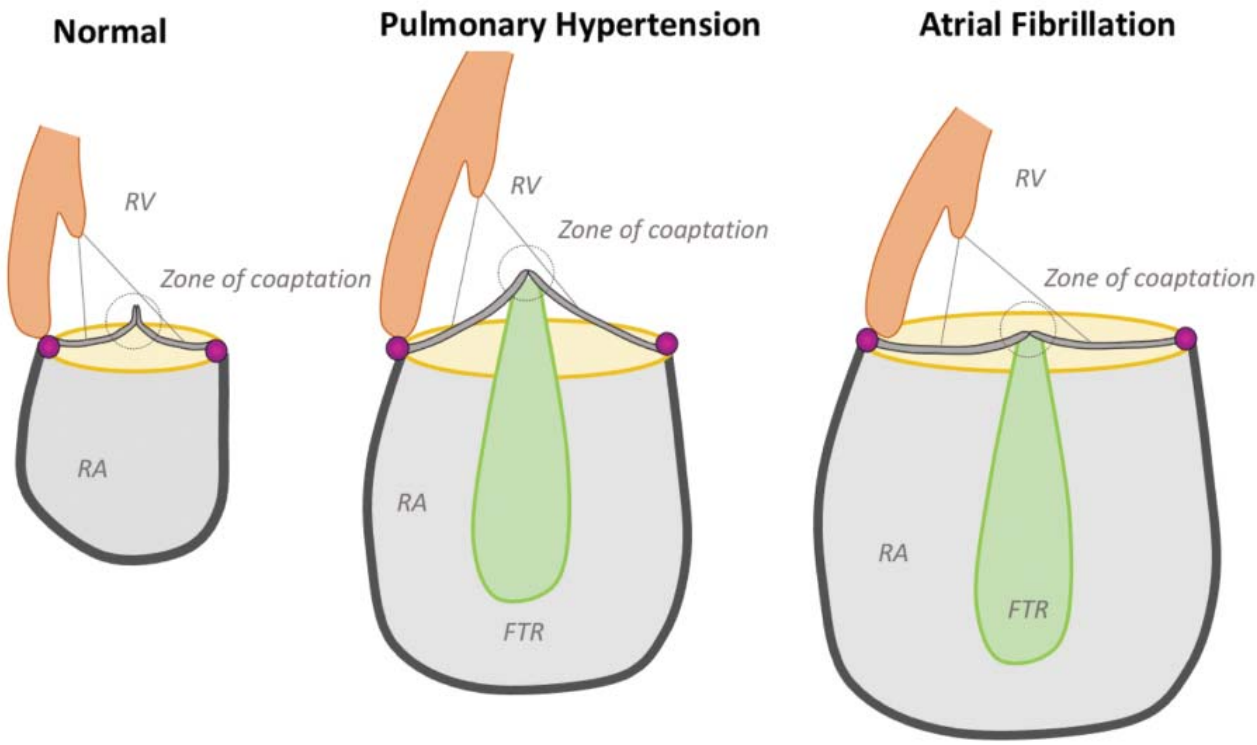


Figure 5. Comparison of the coaptation of the tricuspid leaflets in normal subjects, with the leaflets coapting along the leaflet's body and in the plane of the tricuspid annulus (left panel); coaptation in pulmonary hypertension patients, with the leaflets coaptation occurring along the leaflets' free edge and being apically displaced (ventricular functional tricuspid regurgitation, middle panel); coaptation in atrial fibrillation patients with reduced leaflet apposition due to significant annular dilation (atrial functional tricuspid regurgitation, right panel). Abbreviations: FTR, functional tricuspid regurgitation; RA, right atrium; RV, right ventricle

tion and accounts for the tethering of all three leaflets, as well as for the enlargement of the annulus area.

Finally, novel quantitative parameters by the 3D color Doppler method have been proposed in the evaluation of FTR severity. 3D vena contracta area, EROA by 3D PISA, and regurgitant volume can be obtained, but their routine use is not recommended due to their limited clinical and prognostic validation[22,41].

CLINICAL IMPLICATIONS AND UNMET NEEDS

The key message for cardiologists and echocardiographers is that atrial TR should nowadays be recognized as one of the potential complications of AF and one of the contributing factors for heart failure symptoms. Up to 25% of patients with non-valvular AF develop significant atrial FTR, with 33% of lone AF cases occurring in young patients[42,43]. The awareness regarding atrial FTR and the known adverse prognostic implications of isolated severe FTR may intuitively justify a more aggressive rhythm control in patients with persistent AF that present an associated FTR. Preliminary reports show that cardioversion in atrial FTR with documented maintenance of sinus rhythm promotes TV annulus and RA reverse remodeling and may significantly reduce the severity of FTR at follow-up[26,44,45].

However, current recommendations are largely based on expert opinion and large-scale studies on the prognostic benefits of rhythm vs rate-control strategy in atrial FTR patients are needed to substantiate specific guideline indications for this subset of patients.

CONCLUSIONS

Functional tricuspid regurgitation is a common finding in several cardiac conditions, either isolated or in association with left-heart valvular diseases. Emerging evidence suggests a novel pathophysiological model of atrial functional tricuspid regurgitation in patients with long-standing AF. Three-dimensional echocardiography has revolutionized the noninvasive imaging of the tricuspid valve apparatus, conferring new insights and better understanding of the pathophysiology of functional tricuspid regurgitation. Awareness about the atrial tricuspid functional regurgitation is key to identify

the appropriate management and treatment strategies for these patients.

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