Clinical Context and Mechanism of Functional Tricuspid Regurgitation in Patients with and without Pulmonary Hypertension

Topilsky et al: Mechanisms of Functional TR

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Abstract

Background—Functional tricuspid regurgitation (FTR) with structurally normal valve is of poorly defined mechanisms. Prevalence and clinical context of idiopathic FTR (without overt TR cause) are unknown.

Methods and Results—To investigate prevalence, clinical context and mechanisms specific to FTR-types, idiopathic (Id-FTR) vs. pulmonary hypertension-related (PHTN-FTR, systolic-pulmonary-pressure≥50 mmHg), we analyzed 1161 patients with prospectively quantified TR. Id-FTR (prevalence 12%) was associated with aging and atrial fibrillation (AFib). For mechanistic purposes, we measured valvular and right ventricular (RV) remodeling in 141 Id-FTR matched to 140 PHTN-FTR and to 99 controls with trivial TR for age, sex, AFib and ejection fraction. PHTN-FTR and Id-FTR were also matched for TR effective-regurgitant-orifice (ERO). Id-FTR valvular alterations (vs. controls) were largest annular area (3.53±0.6 vs. 2.74±0.4 cm², p<0.0001) and lowest valvular/annular coverage ratio (1.06±0.1 vs. 1.45±0.2, p<0.0001) but normal valve tenting-height. PHTN-FTR had mild annular enlargement but excessive valve tenting-height (0.8±0.3 vs. 0.35±0.1 cm, p<0.0001). Valvular changes were linked to specific RV changes, largest basal dilatation and normal length (RV conical deformation) in Id-FTR vs. longest RV with elliptical\spherical deformation in PHTN-FTR. With increasing FTR severity (ERO≥40 mm²), changes specific to each FTR-type were accentuated and RV function (index of myocardial performance) was consistently reduced.

Conclusions—Id-FTR is frequent, linked to aging and AFib, can be severe and is of unique mechanism. In Id-FTR, excess annular and RV-basal enlargement exhausts valvular/annular coverage reserve and RV conical deformation does not cause notable valvular tenting. Conversely, PHTN-FTR is determined by valvular tethering with tenting linked to RV elongation and elliptical\spherical deformation. These specific FTR-mechanisms may be important in considering surgical correction in FTR.

Key Words: tricuspid regurgitation, echocardiography, pulmonary hypertension, atrial fibrillation
Tricuspid regurgitation (TR) can be caused by organic valve diseases but often occurs on structurally normal tricuspid valves, called functional TR (FTR). Because of long-recognized relationship between FTR and left-sided cardiac or pulmonary diseases, the link FTR-excessive afterload of pulmonary hypertension (PHTN) is construed as core FTR mechanism and is the main focus of guidelines for valve diseases. However, FTR remains a frustrating condition, poorly understood. Epidemiological studies uncovered TR high prevalence, even without PHTN and conversely, severe PHTN does not necessarily cause notable FTR. Accruing reports noted FTR with normal pulmonary pressure and without overt cause despite comprehensive workup referred as idiopathic FTR (Id-FTR). Idiopathic-FTR prevalence, clinical context and mechanisms are unknown underscoring the general need for better FTR mechanisms understanding. Previous studies implicated various candidate FTR-mechanisms, annular or valvular but uncertainty persists on processes yielding FTR, particularly when severe. This issue is clinically important because severe TR may portend poor prognosis and its treatment with valve repair is mired by frustrating failures poorly understood.

In defining FTR mechanism, previous studies were hindered by heterogeneity of causes and patients’ characteristics when all TR-types are amalgamated. Paucity of comprehensive quantitative assessment of right ventricular (RV) characteristics, valvular alterations and TR severity (particularly with physiologic measures such as effective regurgitant orifice-ERO) also prevent examination of quantitative links between FTR degree and valvular-ventricular-complex alterations. However, these hindrances can now be addressed, starting with careful selection of FTR-types examined. Recent advances in noninvasive Doppler-echocardiography allow consistent measurement of regurgitant volume and ERO providing important insights into TR pathophysiology. Quantification of valvular-ventricular complex deformation, which provided crucial information in functional mitral regurgitation can also be obtained in FTR simultaneously to TR quantitation. Thus, to gain mechanistic insights specific to each FTR-type, we analyzed our prospectively quantified TR population in whom comprehensive imaging of
RV, RA and tricuspid valvular complex had also been performed. We examined prevalence and characteristics of FTR-types and then matched these FTR-types to analyze mechanistic features. We hypothesized that mechanisms linking valvular alterations and RV remodeling to FTR quantified degree are different in patients with idiopathic FTR versus those with TR related to PHTN (PHTN-FTR).

Methods

Design

The study was designed with two aims. First, among patients enrolled in prospective TR quantitation, we assessed Id-FTR prevalence and clinical context with etiologic stratification of all patients, emphasizing those classified as Id-FTR, and ascertaining absence of any known TR cause. Second, for FTR mechanism, Id-FTR, PHTN-FTR groups and control-group with physiologic-trivial TR, strictly matched for baseline characteristics were compared for detailed valvulo-ventricular characteristics. Computer-generated frequency-matching, involved dynamic bins of potential controls and produced groups (not pairs) similar to Id-FTR group for the pre-defined baseline characteristics (see below) from the 336 available of PHTN-FTR with prospectively quantified TR. Frequency matching to Id-FTR was also applied for normal controls with measurable TR velocity examined during the same period. This matching process allowed quantitative direct comparison of RV, RA and valvulo-ventricular complex differences.

Eligibility

For defining prevalence and context of Id-FTR, we analyzed all patients without pericardial or endocardial disease in whom prospective TR quantitation was performed between 1995 and 2005. For defining specific mechanisms of Id-FTR (vs. PHTN-FTR), eligibility criteria were 1) presence of FTR characterized by structurally normal tricuspid leaflets (no organic valve disease), 2) measurable systolic pulmonary artery pressure (SPAP) based on clearly defined TR signal by continuous-wave-
Doppler and inferior vena cava size and respiratory variation, 3) absence of overt left ventricular systolic dysfunction (ejection fraction-EF$\geq$50% in all patients), 4) absence of pace-maker or defibrillator wire across tricuspid valve 5) absence of congenital, pericardial, endocardial or other valve disease, 6) TR holosystolic and prospectively quantified, and 7) high-quality imaging allowing quantitation of RV, RA and tricuspid valvular complex. Age, sex, symptoms and atrial fibrillation (AFib) were not exclusion criteria. There were 141 patients labeled Id-FTR with no detectable TR cause (even after echocardiographic re-review) and without likely pulmonary hypertension by current guidelines (SPAP<50mmHg). We frequency-matched for age, sex, EF, AFib, and TR effective regurgitant orifice area (ERO) these patients with Id-FTR to 140 patients with FTR similarly quantified and likely pulmonary hypertension (SPAP$\geq$50 mmHg) computer-selected from all those with PHTN-FTR (n=336). Patients with Id-FTR were also matched for age, sex, AFib and EF to controls (99 patients) with normal Doppler-Echocardiography and TR trivial (jet less than 1.0 cm$^2$, ERO=0) but with peak velocity clearly measurable to calculate SPAP and exclude likely pulmonary hypertension (SPAP<50 mmHg). Thus, all 380 patients in this mechanistic analysis had EF$\geq$50%, structurally normal tricuspid valve, and FTR by Doppler-echocardiography. The study was powered (80%, 0.05) to detect at least 30% difference in tricuspid annulus diameter and tenting height between patients with and without PHTN.

**Doppler- Echocardiography**

Comprehensive Doppler-Echocardiography was performed in patients instructed to breathe normally. All TR, RV and RA measurements were averages of inspiratory and expiratory measurements over $\geq$5 cardiac cycles.

*Hemodynamic assessment:* SPAP was estimated using continuous-wave-Doppler and inferior vena cava diameter and respiratory variation. Forward stroke volume, cardiac output and index were calculated using pulsed-Doppler.

*Valvular-ventricular-complex assessment* used current recommendations. From 4-chamber views
encompassing the entire RV, end-systolic and end-diastolic RV areas, length, mid-ventricular and basal diameters were measured. RV shape ratios, basal to mid ventricle diameter and RV sphericity index (mid-diameter*length)/(basal-diameter), were calculated in systole (after tricuspid closure). RV free-wall thickness and outflow tract diameter were measured. RV function was evaluated by RV end-systolic area, fractional area change (fractional-shortening) and index of myocardial performance (RIMP). Tricuspid annulus systolic and diastolic diameters (%contraction calculated) and systolic valve tenting height and area were measured. Tricuspid leaflets length (septal+anterior leaflets) was measured and ratio to systolic annulus diameter calculated to assess valvular coverage of annulus in systole. RA end-systolic area and length allowed RA volume calculation using area-length formula. Cavity areas and diameters were normalized to body surface area.

TR assessment used color-flow-imaging and quantitative measures. TR color-jet area was planimetered and ratio to RA area calculated. TR quantitation used proximal flow convergence (PISA) as validated (Figure 1). Corrections for leaflets-angle and TR velocity allowed calculation of regurgitant flow (RFlow), ERO area (RFlow/velocity) and regurgitant volume (RVol). TR duration was measured directly using Doppler signal.

Statistical analysis

Results were expressed as mean±SD or percentages. Group comparisons used ANOVA and Tuckey-Kramer test for post-hoc multiple comparisons. Associations between morphology and FTR-severity were analyzed univariously by classifying patients as trivial-TR (ERO=0), mild-moderate TR (ERO 1-39 mm2) and severe-TR (ERO≥40 mm2). Intragroup (Id-FTR or PHTN-FTR) univariable associations with ERO were analyzed including controls-TTR patients and testing for trends. Multivariable analyses used logistic regression models with ERO≥40 mm2 as dependent variable including interaction terms for FTR-types and analyses within FTR-type. RV characteristics association with >median tenting height (0.6cm) and >median valvular/annular ratio (1.1) used similar sequence. All multivariable models were
adjusted for age, sex and AFib. Inter-observer and intra-observer variability, in 11 random patients with
blinded measurements, used paired t-test, Bland-Altman plotting and concordance coefficient of
correlation (CCC). P<0.05 was considered significant. Analyses were performed with SAS version 9.2

Results
Burden and Clinical context of Idiopathic FTR

The 1161 patients examined prospectively and quantitatively for TR were classified etiologically in
sequential manner. Traditional causes included 4 groups, congenital TR (any congenital heart disease
resulting in TR including ASD), organic or pacemaker/defibrillator-associated TR (TR without
congenital disease associated with structural tricuspid disease or a lead penetrating the tricuspid orifice),
TR with left-sided valvular disease ≥moderate and TR with left ventricular systolic dysfunction
(EF<50%). Remaining patients had FTR classified PHTN-linked with SPAP≥50mmHg or Id-FTR with
SPAP<50mmHg. Prevalence of TR etiologies was: TR associated with congenital diseases 8.9%,
organic/pacemaker TR 11.9%, TR of left valvular disease 25.9% and TR of left ventricular systolic
dysfunction 12.2%. Thus, traditional causes of TR (congenital, organic, left-valvular, and left ventricular
dysfunction) represented 58.9% of patients. PHTN-FTR involved 28.9% and Id-FTR 12.2%. TR causes
were similarly distributed in our community (Olmsted County, MN) or distantly-referred (p=0.35).
Clinical context, comparing Id-FTR vs. PHTN-FTR vs. traditional TR causes, showed Id-FTR associated
with older age (71.5±13.8 vs. 67.4±16.5 vs. 61.6±20.8 years respectively; p<0.0001-all comparisons),
female sex (69.5% vs. 71.0% and 54.7% respectively; p<0.0001) and AFib at diagnosis (51.0% vs. 19.1%
vs. 11.5%; p<0.0001). AFib prevalence was higher in Id-FTR whether TR was severe (ERO≥40mm²,
57.3% vs. 23.0% vs. 14.8%; p<0.0001) or less severe (ERO<40mm², 38.4% vs. 16.0% vs. 7.2%;
p<0.0001). Thus, Id-FTR link to aging and AFib underscores the importance of appropriate matching vs.
PHTN-FTR for TR mechanistic analysis.

**Mechanistic Matched Analysis: Baseline Characteristics**

The mechanistic analysis included 380 patients with FTR, ranging from trivial to severe (Table 1). Comparison between groups verified that matching was successful. By design, SPAP was higher in PHTN group but SPAP and TR velocity were similar (Table 2) in Id-FTR and controls-TTR. Although not part of matching, blood pressure, heart rate or cardiac index displayed no difference between groups. Thus, matching achieved groups similar in many aspects and with specific crucial differences: Id-FTR and PHTN-FTR had similar ERO (p=0.34) and differed essentially by likely PHTN. Id-FTR and control-TTR and had identical AFib prevalence and differed essentially by FTR degree. Observer variability was low for all measurements (all p>0.23) with all CCC ≥ 0.70.

**Contrasting TR characteristics by FTR-types**

TR and associated RV and RA characteristics are listed in Table 2. By design, ERO matched between Id-FTR and PHTN-FTR and was assigned null value in controls-TTR (ERO=0). However, RVol was higher in PHTN-FTR vs. Id-FTR due to larger driving force (pressure) and TR duration. Higher TR flow and velocity in PHTN-FTR resulted in larger jet and jet/RA ratio than in Id-FTR. Volume overload yielded larger diastolic RV size in Id-FTR vs. controls-TTR and even larger in PHTN-FTR.

Variables measuring RV function showed complex changes. In Id-FTR, RV end-systolic enlargement was concordant with decreased fractional-shortening and increased RIMP vs. controls-TTR despite similar SPAP, demonstrating serious RV function alterations. Conversely, in PHTN-FTR, variables measuring RV function are discordant, with RV fractional-shortening similar to controls-TTR but with higher RV end-systolic size and RIMP emphasizing incipient RV dysfunction. Larger RA in Id-FTR and PHTN-FTR vs. controls-TTR demonstrates RA distention linked to FTR beyond the similarly prevalent AFib. FTR-types were stratified according to FTR severity (ERO ≥ 40mm2) in Table 3. With severe FTR, RV enlarged in both groups but RV fractional-shortening declined in Id-FTR vs. maintained in
PHTN-FTR (p=0.0002) although similarly increased RV end-systolic size and RIMP, suggest similar RV function alterations. Thus, serious RV and RA consequences are markedly influenced by FTR-type (PHTN-FTR vs. Id-FTR).

**Contrasting alterations of valvular-ventricular complex by FTR-types**

Valvular alterations by FTR-types are shown Figure 2, overall and are stratified by ERO (<40 or ≥40 mm²) Table 3. Tricuspid annulus systolic dimension (Figure 2, Panel A) is increased in both FTR-types vs. controls-TTR but larger in Id-FTR vs. PHTN-FTR even after stratification by ERO (Table 3). Conversely, leaflet-length is similar in controls-TTR, Id-FTR and PHTN-FTR (2.11±0.34 vs. 2.06±0.30 vs. 2.12±0.31 cm/m², p=0.26). Thus, systolic annulus coverage by leaflets (Figure 2, Panel C) is highest in controls and lowest in Id-FTR even after stratification by ERO (Table 3). Ventricular displacement of leaflets (tenting height, Figure 2, panel B) is not exaggerated vs. controls-TTR in Id-FTR but is markedly exaggerated in PHTN-FTR even after stratification by ERO (Table 3). Thus, more severe PHTN-FTR is characterized by more tenting height, in contrast to Id-FTR. Conversely, increased tenting area reflects both larger annulus and tenting height and thereby is not discriminant.

In multivariable analysis (entire population) adjusting for age, sex and AFib, tenting height (p<0.0001) and leaflet/annulus ratio (p=0.0002) were independently associated with ERO≥40 mm² (AUC 0.79). However, there was significant interaction between ERO determinants and FTR-type (p<0.0001). Indeed, the only independent ERO valvular-determinants are lower leaflet/annular ratio in Id-FTR (p<0.0001, AUC 0.90) and higher tenting height in PHTN-FTR (p<0.0001, AUC 0.86). In 11 patients with Id-FTR who underwent tricuspid valve surgery (4 replacements, 7 repairs), direct valve inspection showed in all marked annular dilatation with normal valve tissue gross appearance.

RV morphology (Figure 3 and 4 and Table 3) was different between FTR-types. Although RV was enlarged in both FTR-types, RV length was not increased in Id-FTR vs. controls-TTR but was markedly increased in PHTN-FTR (Figure 4, panel C) particularly severe PHTN-FTR (Table 3). Mid-RV diameters
are similarly increased in Id-FTR and PHTN-FTR but basal-RV diameters are considerably increased in Id-FTR and only slightly in PHTN-FTR (Figure 4, panels B and A). Thus, ratio of RV basal diameter to length (Figure 4 panel E) and ratio of RV basal to mid-ventricular diameter (Table 3) are highest in Id-FTR, consistent with RV conical deformation (vs. controls). Conversely, lowest ratio of RV basal to mid-ventricular diameter and highest sphericity index in PHTN-FTR are consistent with RV elliptical/spherical deformation (vs. controls). RV shape and size changes in PHTN-FTR and Id-FTR vs. controls are schematically presented Figure 5. RV changes independently determine valvular changes in multivariable analysis. In PHTN-FTR higher RV sphericity (p<0.0001) and RIMP (p=0.007) are independently associated with tenting-height≥0.6cm (AUC 0.88) and higher RVol (both p<0.001).

Conversely, in Id-FTR higher RV basal/length ratio is the only RV characteristics independently linked to leaflet/annular ratio<1.1 (p<0.0001, AUC 0.88). RV wall thickness was highest in PHTN-FTR (Figure 4, panel D) as expected.

Discussion

The present series of consecutively and prospectively quantified TR shows that Id-FTR represents about 12% of patients with TR. Irrespective of classification chosen to assess TR-etiologies, Id-FTR is without any known cause but shows a strong link to aging and AFib. Mechanistic analysis based on comprehensive quantitation of TR, RV, RA and valvular-ventricular complex and matching of baseline characteristics between FTR-types provides important insights into FTR mechanisms and pathophysiology. FTR with or without PHTN can be severe and lead to untoward consequences, with RV dilatation and increased end-systolic RV size and RIMP suggesting universally reduced RV function with increasing FTR severity. FTR mechanisms are different in Id-FTR and PHTN-FTR despite similar ERO (valve lesion) with specific valvular-ventricular complex alterations. Id-FTR main valvular mechanism is exhaustion of annular coverage reserve by tricuspid leaflets due to marked annular...
enlargement, but valvular tenting plays no or minimal role. PHTN-FTR main mechanism is valvular tethering with tenting above annular level reducing coaptation but annular enlargement is modest. These contrasting valvular mechanisms determining directly FTR severity are associated with specific RV remodeling patterns. In PHTN-FTR, the RV is not only larger, but also longer with more elliptical/spherical deformation and more RV deformation is linked to higher valve tenting and thereby, larger ERO. Conversely, in Id-FTR RV shows conical deformation without elongation and with larger RV base. Wider RV base and annulus are linked to lower valvular-annular coverage and larger ERO. Thus, FTR is not uniform and the TR, RV and valvular-ventricular complex characteristics are specific to each FTR-type. Thus, in clinical practice, TR severity and characteristics should be fully described and integrated into clinical decision-making regarding FTR treatment.

**Importance of Functional Tricuspid Regurgitation**

Management of severe tricuspid regurgitation (TR) is complex and mired by frustration. Doppler-Echocardiography often shows a structurally normal tricuspid valve associated with TR. Clinical significance and management of TR remain uncertain but recent series suggest that TR and particularly FTR impact seriously outcome a concept vetted by recent reviews. FTR importance is supported by Id-FTR notable prevalence, 12% of this quantified population (after extensive verification that other TR causes were not ignored), which is not a referral artifact. Id-FTR link to aging and AFib suggests a growing burden, which combined with PHTN-FTR frequency, warrants precisely delineating FTR mechanisms to ultimately improve FTR treatment. Relatively small series, lack of quantitative assessment and multiplicity of “causes” hindered mechanistic analyses. To address this vexing issue, we took advantage of prospective efforts at quantifying TR, strictly defined patients’ subsets and carefully matched FTR-types.

**Valvular Mechanism of Functional Tricuspid Regurgitation**

FTR was considered as one entity with annular dilatation as core mechanism and possible but
uncertain contributing role of leaflet tethering.\textsuperscript{16,17,40} RV remodeling contribution to FTR development is also controversial.\textsuperscript{6,8,16,38} Our study shows that valvular determinants of FTR lesion severity (ERO) are specific to each FTR type. In Id-FTR, exhaustion of the valvular coverage reserve of the excessively dilated annulus mainly determines TR severity. Considerable annular dilatation is required for incomplete tricuspid coaptation\textsuperscript{15} because substantial redundancy of leaflet tissue prevents TR\textsuperscript{3} in normal tricuspid valves (ratio leaflets/annular length 1.45). With severe Id-FTR (ERO\textsuperscript{•}0.4 cm\textsuperscript{2}) leaflet coverage declined markedly with decreasing coaptation not due to retracted leaflets, as available valvular tissue was similar in all subsets. The Id-FTR entity is not well known, not only mechanistically but also clinically, and awareness of its existence was raised by few seminal reports.\textsuperscript{9,11,12,14} While our data highlight Id-FTR exhaustion of valvular reserve in covering the enlarged tricuspid annulus, the cause of annular enlargement remains uncertain. AFib association suggests links to atrial enlargement\textsuperscript{11} but Id-FTR also occurs in sinus rhythm and its link to aging may reflect annular degeneration. Among 11 Id-FTR patients who underwent TR surgery, three underwent RA and AV groove biopsy showing interstitial fibrosis with mild myocyte hypertrophy. These non-specific observations incite further tissue analysis of tricuspid annulus to uncover biological mechanisms of Id-FTR.

Conversely, in PHTN-FTR, annular dilatation, while present, is less impressive and tricuspid annulus coverage is closer to normal. Thus, another factor causing TR is required to explain the ERO similar to Id-FTR. In PHTN-FTR, leaflet deformation with increased tenting height\textsuperscript{40} and intra-ventricular leaflets’ displacement, preventing appropriate coaptation \textsuperscript{39} is the main determinant of ERO. Thus, our quantitative data show that Id-FTR and PHTN-FTR result from two distinct mechanisms, exhaustion of leaflet coverage reserve in Id-FTR and leaflet deformation with tenting in PHTN-FTR.

**Right Ventricular alterations in Functional Tricuspid Regurgitation**

RV remodeling occurs in both FTR-types with RV dilatation associated to volume overload vs. controls-TTR. However, despite similar regurgitant lesion (ERO) by design, patients with PHTN-FTR vs. Id-FTR
incur larger RVol, due to inherent hemodynamic differences (greater TR duration and driving force) and larger RV diastolic volume. This difference in RV volume overload affects RV function assessment. In Id-FTR there is concordant alteration of RV function indices with increasing TR severity. In PHTN-FTR, with large volume overload RV fractional-shortening remains high and RV dysfunction may be undetected by casual examination. Furthermore, RV remodeling is radically different in Id-FTR and PHTN-FTR despite similar ERO with valvular-ventricular complex alterations specific of each FTR type. In Id-FTR, RV displays conical deformation with concordant RV basal and annular enlargement while RV length is not affected. This type of RV remodeling cannot cause apical or lateral displacement of tricuspid papillary muscles and we found no evidence of valvular tethering. Consequently, valve tenting height is not different from controls and larger tenting area is purely linked to annular enlargement.

Conversely in PHTN-FTR, RV basal and tricuspid annular dilatations, although present, were unrelated to FTR severity and RV was elongated with spherical elliptical deformation. These RV changes specific of PHTN-FTR tend to eccentrically displace the tricuspid papillary muscles, laterally and apically and in view of chordal inextensibility are logically linked to tricuspid leaflet tethering and apical tenting. Thus, despite substantial leaflet availability for annulus coverage, systolic valve deformation with tenting of PHTN reduces tricuspid coaptation yielding similar ERO in PHTN-FTR and Id-FTR. Therefore, in each FTR-type concordant ventricular-valvular complex alterations explain very different FTR-mechanisms in Id-FTR vs. PHTN-FTR.

**Study Limitations**

TR cause classification may be disputed but Id-FTR has no overt cause, irrespective of classifications. Id-FTR may be doubted but in those who underwent tricuspid surgery, absence of known TR cause and marked annular dilatation were confirmed by direct visualization. Matching by ERO, warranted to compare Id-FTR and PHTN-FTR differing mechanisms leading to similar lesion severity, implies larger RVol and RV volumes in PHTN-FTR due to afterload differences. Future studies should analyze
whether RVol-matching is associated with differing RV size, shape and function.

Echo-Doppler methods may be criticized. The PISA method to quantify TR has not been used as widely as for other regurgitations\textsuperscript{28} but has been validated\textsuperscript{29} and confirmed by our institution and others\textsuperscript{27}.

Assessing RV remodeling is complex but was based on current guidelines.\textsuperscript{32,33} SPAP determination using TR signal may be criticized but allows to reliably classify patients with and without likely PHTN\textsuperscript{42} and is the basis of clinical guidelines.\textsuperscript{4} If Id-FTR focused only on unlikely PHTN (SPAP\textless 36 mmHg)\textsuperscript{4} FTR severity determinants remained unchanged (Leaflet/Annular ratio determines ERO, p<0.0001 AUC 0.96; RV basal/length ratio strongly associated to Leaflet/Annular ratio, p<0.0001, AUC 0.87). Thus, exact boundaries of Id-FTR definition do not affect mechanistic analysis results.

**Conclusions**

Our quantitative study shows that FTR is frequent and that idiopathic-FTR represents a notable proportion, may be severe and is strongly associated to aging and atrial fibrillation. Comprehensive quantitation also shows that FTR is a complex entity with contrasting mechanisms depending on FTR-type. Idiopathic FTR is related to tricuspid annular dilatation with exhaustion of leaflet annular coverage reserve and with little or no role for leaflet tenting in the loss of coaptation leading to severe TR. In Id-FTR, RV basal dilatation without elongation results in RV conical deformation. Conversely, PHTN-FTR is predominantly due to valve deformation with tenting and only modest annular enlargement. Valvular tenting and leaflet tethering are linked to RV elongation and elliptical\textbackslash spherical deformation. Hence, RV remodeling and functional response to volume\textbackslash pressure overload are complex and differ widely depending on FTR-type. These mechanistic insights provide important clues on FTR development and on potential approaches to surgical correction.
Disclosures

Dr Enriquez-Sarano discloses a research grant funding from Abbott Laboratories. No other disclosure was reported.

References


Table 1. Baseline characteristics of patients overall and stratified by functional tricuspid regurgitation type.

<table>
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<tr>
<th>Groups</th>
<th>Characteristics</th>
<th>All Patients</th>
<th>Controls-TTR (N=99)</th>
<th>Id-FTR (N=141)</th>
<th>PHTN-FTR (N=140)</th>
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<td>Age, years</td>
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<td>71.2±14.0</td>
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<td>71.4±13.9</td>
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<td>Atrial fibrillation, (%)</td>
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<td>Gender, (% males)</td>
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<td>32.3</td>
<td>31.2</td>
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<td>EF, %</td>
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<td>SBP, mmHg</td>
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<td>HR</td>
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<td>CI, L·min(^{-1})·m(^2)</td>
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<td>SPAP, mmHg</td>
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<td>32.5±6.5</td>
<td>39.6±6.9</td>
<td>71.5±20.6**†‡</td>
<td>&lt;0.0001</td>
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EF: Ejection Fraction; SBP: Systolic Blood Pressure; HR: Heart Rate; CI: Cardiac Index; TR: Tricuspid Regurgitation; TTR: Trivial (physiologic) TR; Id-FTR: Idiopathic Functional TR; PHTN-FTR: Functional TR due to pulmonary hypertension; SPAP: Systolic Pulmonary Artery Pressure.

*P<0.05 vs. Controls TTR, ** P<0.001 vs. Controls-TTR, † P<0.05 vs. Id-FTR, ‡ P<0.001 vs. Id-FTR
Table 2. Characteristics of tricuspid regurgitation and right ventricle stratified by functional tricuspid regurgitation type.

<table>
<thead>
<tr>
<th>TR Characteristics</th>
<th>Etiologic groups of Functional TR (FTR)</th>
<th>P value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls-TTR</td>
<td>Id-FTR</td>
</tr>
<tr>
<td>N</td>
<td>99</td>
<td>141</td>
</tr>
<tr>
<td>TR Velocity, m/s</td>
<td>2.54±0.3</td>
<td>2.68±0.3</td>
</tr>
<tr>
<td>TR Duration, msec</td>
<td>397.2±55.8</td>
<td>407.6±50.8</td>
</tr>
<tr>
<td>TR ERO, mm²</td>
<td>0</td>
<td>47±33**</td>
</tr>
<tr>
<td>TR RVol. mL/beat</td>
<td>0</td>
<td>37.0±19.5**</td>
</tr>
<tr>
<td>TR jet area, cm²</td>
<td>&lt;1.0</td>
<td>8.4±4.6**</td>
</tr>
<tr>
<td>TR jet/RA area ratio, %</td>
<td>&lt;5.0</td>
<td>41±19**</td>
</tr>
<tr>
<td>RV-EDA index, cm²/m²</td>
<td>12.2±2.6</td>
<td>15.4±4.5**</td>
</tr>
<tr>
<td>RV-ESA index, cm²/m²</td>
<td>6.9±1.6</td>
<td>9.6±3.4**</td>
</tr>
<tr>
<td>RV-AFS, %</td>
<td>41.9±10.6</td>
<td>37.5±10.9*</td>
</tr>
<tr>
<td>RIMP ratio</td>
<td>0.31±0.16</td>
<td>0.42±0.18**</td>
</tr>
<tr>
<td>RA volume index, mL/m²</td>
<td>26.2±8.8</td>
<td>46.7±23.8**</td>
</tr>
</tbody>
</table>

TTR: Trivial Tricuspid Regurgitation; Id-FTR: Idiopathic Functional Tricuspid Regurgitation; PHTN-FTR: Pulmonary Hypertension related Functional Tricuspid Regurgitation; ERO: Effective Regurgitant Orifice; RVol: Regurgitant Volume; RAP: Right Atrial Pressure; RVSP: Right Ventricular Systolic Pressure; RV-EDA: Right Ventricular End Diastolic area (4 chamber view); RV-ESA: Right Ventricular End Systolic Area (4 chamber view); RV-AFS: Right Ventricle Area Fractional Shortening; RIMP: Right Index of Myocardial Performance.

*P<0.05 vs. Controls-TTR, **P<0.001 vs. Controls-TTR, †P<0.05 vs. Id-FTR, ‡P<0.001 vs. Id-FTR
Table 3. RV, RA dimensions, and valvular alterations, stratified by TR severity and functional regurgitation type.

<table>
<thead>
<tr>
<th>Control-TTR (N=99)</th>
<th>ERO &lt;40mm²</th>
<th>ERO ≥40mm²</th>
<th>P for trend</th>
<th>ERO &lt;40mm²</th>
<th>ERO ≥40mm²</th>
<th>P for trend</th>
<th>P for trend vs. Id-FTR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVol, mL</td>
<td>0</td>
<td>25±8</td>
<td>53±18</td>
<td>&lt;0.0001</td>
<td>38±12</td>
<td>67±28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV-EDA index cm²/m²</td>
<td>12.1±2.6</td>
<td>13.9±3.3</td>
<td>17.2±5.1</td>
<td>&lt;0.0001</td>
<td>15.3±4.0</td>
<td>18.5±7.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV-ESA index cm²/m²</td>
<td>6.9±1.6</td>
<td>8.5±2.4</td>
<td>10.9±4.0</td>
<td>&lt;0.0001</td>
<td>8.9±3.3</td>
<td>10.7±6.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RIMP ratio</td>
<td>0.31±0.16</td>
<td>0.41±0.17</td>
<td>0.44±0.19</td>
<td>0.0003</td>
<td>0.43±0.18</td>
<td>0.51±0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA volume index, cm³/m²</td>
<td>41.9±10.6</td>
<td>38.5±11.1</td>
<td>36.2±10.7</td>
<td>0.002</td>
<td>41.8±11.6</td>
<td>42.3±13.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Tenting area, cm²</td>
<td>0.48±0.18</td>
<td>0.73±0.6</td>
<td>0.87±0.47</td>
<td>&lt;0.0001</td>
<td>1.14±0.52</td>
<td>1.38±0.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ann-4C diastolic diameter, cm</td>
<td>3.3±0.5</td>
<td>4.2±0.7</td>
<td>4.7±0.7</td>
<td>&lt;0.0001</td>
<td>3.6±0.6</td>
<td>3.9±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ann-4C systolic diameter, cm</td>
<td>2.74±0.36</td>
<td>3.4±0.6</td>
<td>3.7±0.6</td>
<td>&lt;0.0001</td>
<td>3.2±0.56</td>
<td>3.4±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ann-4C systolic contraction, %</td>
<td>15.8±8.9</td>
<td>18.4±11.5</td>
<td>19.6±9.6</td>
<td>0.18</td>
<td>11.2±12.1</td>
<td>12.3±11.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Leaflet length index, cm/m²</td>
<td>2.1±0.3</td>
<td>2.1±0.3</td>
<td>2.0±0.3</td>
<td>0.09</td>
<td>2.1±0.3</td>
<td>2.1±0.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Leaflet/annular ratio</td>
<td>1.45±0.2</td>
<td>1.11±0.11</td>
<td>1.00±0.09</td>
<td>&lt;0.0001</td>
<td>1.26±0.21</td>
<td>1.20±0.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV basal diameter index cm/m²</td>
<td>1.7±0.20</td>
<td>2.4±0.3</td>
<td>2.6±0.5</td>
<td>&lt;0.0001</td>
<td>1.9±0.3</td>
<td>2.1±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV mid cavitary index cm²/m²</td>
<td>1.8±0.3</td>
<td>2.2±0.3</td>
<td>2.5±0.5</td>
<td>&lt;0.0001</td>
<td>2.2±0.4</td>
<td>2.5±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV length index cm²/m²</td>
<td>4.1±0.5</td>
<td>4.1±0.5</td>
<td>4.4±0.6</td>
<td>0.01</td>
<td>4.4±0.5</td>
<td>4.8±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVO, diameter index cm²/m²</td>
<td>1.8±0.3</td>
<td>2.1±0.3</td>
<td>2.2±0.4</td>
<td>&lt;0.0001</td>
<td>2.1±0.3</td>
<td>2.2±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV wall thickness index mm/m²</td>
<td>3.1±0.6</td>
<td>3.3±0.7</td>
<td>3.4±0.8</td>
<td>0.09</td>
<td>4.7±0.9</td>
<td>5.2±1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basal/Mid cavitary ratio</td>
<td>0.97±0.1</td>
<td>1.07±0.12</td>
<td>1.07±0.12</td>
<td>&lt;0.0001</td>
<td>0.87±0.13</td>
<td>0.86±0.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV sphericity index*</td>
<td>8.1±1.2</td>
<td>6.9±1.1</td>
<td>7.6±1.3</td>
<td>0.05</td>
<td>9.9±2.1</td>
<td>10.9±3.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

TTR: Trivial Tricuspid Regurgitation; Id-FTR: Idiopathic Functional Tricuspid Regurgitation; PHTN-FTR: Pulmonary Hypertension related Functional Tricuspid Regurgitation; Ann-4C: Tricuspid annulus in 4 chamber view; ERO: Effective Regurgitant Orifice; RA: Right Atrium; RV: Right Ventricle; RV-EDA, RV-ESA: Right Ventricular End Diastolic and End Systolic Areas (4 chamber view); RV-AFS: Right Ventricle Area Fractional Shortening; RIMP: Right Index of Myocardial Performance.

† P for difference in trend between PHT-FTR and Id-FTR

* RV mid diameter and length product divided by basal diameter.
**Figure Legends**

**Figure 1.** Examples of valvular alterations in Functional Tricuspid Regurgitation. Panels A and B show the tricuspid valve deformation with annular dimensions marked by the white line and valvular tenting (T). Panels C and D show the large proximal flow convergence for the same patients appearing in yellow after down-shift of color baseline. Panels A and C correspond to idiopathic functional tricuspid regurgitation; Panels B and D correspond to functional tricuspid regurgitation with pulmonary hypertension. RV, RA right ventricle and atrium.

**Figure 2.** Valvular alterations in patients with Functional Tricuspid Regurgitation (FTR) according to FTR-type, idiopathic (Id-FTR) vs. related to pulmonary hypertension (PHTN-FTR). The variables represented are tricuspid annular diameter (Panel A), tricuspid valve tenting height (Panel B) and the ratio of tricuspid leaflet length to annular diameter (Panel C). Id-FTR displays marked annular dilatation, low tenting height, and low leaflet tissue coverage of the enlarged annulus. Conversely, PHTN-FTR displays less annular enlargement, but more tenting resulting in similarly poor coaptation.

**Figure 3.** Right ventricular and atrial alterations in two patients with functional tricuspid regurgitation. LV, LA left ventricle and atrium. RV, RA right ventricle and atrium. Panel A corresponds to a patient with idiopathic tricuspid regurgitation and panel B corresponds to patient with tricuspid regurgitation with pulmonary hypertension. Note the considerable dilatation of RV and RA in both cases but with marked differences in RV shape and length between the two patients.

**Figure 4.** Right Ventricular (RV) alterations according to Functional Tricuspid Regurgitation (FTR) type, idiopathic (Id-FTR) vs. related to pulmonary hypertension (PHTN-FTR). The variables are RV basal width (diameter) indexed to body surface area (Panel A), RV mid-cavitary width index (Panel B) RV length index (Panel C) RV wall thickness (Panel D) and RV ratio of basal width to length (Panel E). Id-FTR and PHTN-FTR present different form of RV remodeling: In Id-FTR marked RV basal widening with little lengthening and no wall thickening; In PHTN-FTR less RV basal widening, more lengthening and wall thickening. Thus, RV shape measured by basal-width/length ratio is different in Id-FTR vs. PHTN-FTR
**Figure 5.** Schematic representation of Right Ventricular (RV) and atrial (RA) remodeling and valvular deformation comparing matched normal controls to idiopathic FTR (Id-FTR) vs. related to pulmonary hypertension (PHTN-FTR). In Id-FTR and PHTN-FTR for similar effective regurgitant orifice, similar systolic RV and RA enlargement vs. controls is noted. However, in Id-FTR there is marked tricuspid annular and RV basal widening with normal tricuspid leaflet length resulting in reduced annular coverage in systole. Limited RV lengthening or RV walls centrifugal displacement (“conical” shaped RV) does not cause leaflet tethering and tenting. In PHTN-FTR, there is less annular enlargement and better leaflet coverage, but RV lengthening and eccentricity (elliptical-shaped RV) yields tricuspid leaflets tethering and tenting, with ultimate coaptation loss identical in Id-FTR and PHTN-FTR.
Figure 2

**Annulus Diameter**

- Controls-TTR: 2.74±0.4 cm
- Id-FTR: 3.53±0.6 cm
- PHTN-FTR: 3.3±0.6 cm

**Tenting Height**

- Controls-TTR: 0.42±0.4 cm
- Id-FTR: 0.35±0.1 cm
- PHTN-FTR: 0.42±0.3 cm

**Leaflet/Annulus Ratio**

- Controls-TTR: 1.45±0.2
- Id-FTR: 1.06±0.1
- PHTN-FTR: 1.23±0.2

*P<0.05 vs. TTR, ** P<0.001 vs. TTR         + P<0.05 vs. Id-FTR, ‡ P<0.001 vs. Id-FTR
Figure 3
Figure 4

**P<0.05 vs. TTR, ** P<0.001 vs. TTR  
+ P<0.05 vs. Id-FTR, ‡ P<0.001 vs. Id-FTR
Figure 5

Controls

Id-FTR

PHTN-FTR
Clinical Context and Mechanism of Functional Tricuspid Regurgitation in Patients with and without Pulmonary Hypertension

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