Clinical Context and Mechanism of Functional Tricuspid Regurgitation in Patients With and Without Pulmonary Hypertension

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

Methods and Results—To investigate prevalence, clinical context, and mechanisms specific to FTR types, Id-FTR versus pulmonary hypertension-related (PHTN-FTR, systolic pulmonary pressure ≥50 mm Hg), we analyzed 1161 patients with prospectively quantified TR. Id-FTR (prevalence 12%) was associated with aging and atrial fibrillation. 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, atrial fibrillation, and ejection fraction. PHTN-FTR and Id-FTR were also matched for TR effective-regurgitant-orifice (ERO). Id-FTR valvular alterations (versus controls) were largest annular area (3.53 ± 0.6 versus 2.74 ± 0.4 cm², P < 0.0001) and lowest valvular/annular coverage ratio (1.06 ± 0.1 versus 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 versus 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 versus 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 atrial fibrillation, 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. (Circ Cardiovasc Imaging. 2012;5:314-323.)

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).1 Because of a long-recognized relationship between FTR and left-sided cardiac2,3 or pulmonary1,4 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 diseases5; however, FTR remains a frustrating condition, poorly understood.6 Epidemiological studies uncovered TR with high prevalence, even without PHTN,7 and, conversely, severe PHTN does not necessarily cause notable FTR.8 Accruing reports noted FTR with normal pulmonary pressure9 and without overt cause, despite comprehensive workup,10 referred as idiopathic FTR (Id-FTR).9,11-14 Id-FTR prevalence, clinical context, and mechanisms are unknown, underscoring the general need for better FTR mechanism understanding.1 Previous studies implicated various candidate FTR mechanisms, annular3,15,16 or valvular,16,17 but uncertainty persists on processes yielding FTR, particularly when severe.1 This issue is clinically important because severe TR may portend poor prognosis,18,19 and its treatment with valve repair is mired by frustrating failures,17,20-24 poorly understood.24,25

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In defining FTR mechanism, previous studies were hindered by heterogeneity of causes and patient characteristics when all TR types are amalgamated.26 Paucity of comprehensive quantitative assessment of right ventricular (RV) characteristics, valvular alterations, and TR severity (particularly, with physiological measures such as 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 (RVol) and ERO,27-29 providing important insights into TR pathophysiology.27,30 Quantification of valvular-ventricular complex deformation, which provided crucial information in functional mitral regurgitation,31 can also be obtained in FTR simultaneously to TR quantitation.26 Thus, to gain mechanistic insights specific to each FTR type, we analyzed our prospectively quantified TR population in whom comprehensive imaging of RV, right atrial (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 TR quantified degree are different in patients with id-FTR versus those with TR related to PHTN (PHTN-FTR).

Methods

Design

The study was designed with 2 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 the control-group with physiological-trivial TR, strictly matched for baseline characteristics, were compared for detailed valvular-ventricular characteristics. Computer-generated frequency matching involved dynamic bins of potential controls and produced groups (not pairs) similar to the Id-FTR group for the predefined 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 valvular-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 (versus 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 diameter and respiratory variation, used for TR quantitation used proximal flow convergence (PISA) as validated;27,28 TR function was evaluated by RV end-systolic area, fractional area change (fractional shortening [FS]) and index of myocardial performance (RIMP).35 Tricuspid annulus systolic and diastolic diameters (% contraction calculated)33,34 and systolic valve tenting height and area were measured. Tricuspid leaflets length (septal+anterior leaflets) were 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

TR assessment used color-flow imaging and quantitative measures.27-29 TR color-jet area was planimetered and ratio to RA area was calculated. TR quantitation used proximal flow convergence (PISA) as validated (Figure 1). For TR quantification, patients instructed to breathe normally. All TR, RV, and RA measurements were averages of inspiratory and expiratory measurements before 2 cardiac cycles.

Statistical Analysis

Results were expressed as mean±SD or percentages. Group comparisons used the ANOVA and Tuckey-Kramer test for posthoc multiple comparisons. Associations between morphology and FTR severity were analyzed univariably by classifying patients as Id-FTR (ERO, 0), mild-moderate TR (ERO, 1 to 39 mm²), and severe TR (ERO ≥40 mm²).27 Intragroup (Id-FTR or PHTN-FTR) univariant associations with ERO were analyzed, including controls-TR patients and testing for trends. Multivariable analyses used logistic regression models with ERO ≥40 mm² as dependent variables, including interaction terms for FTR types and analyses within FTR type. RV characteristic association with >median tenting height (0.6 cm) and >median valvular/annular ratio (1.1) used similar sequence. All multivariable models were adjusted for age, sex, and AFib. Interobserver and intraobserver variability, in 11 random patients with blinded measurements, used paired t test, Bland-Altman plotting, and concordance coefficient of correlation. P<0.05 was considered significant. Analyses were performed with SAS version 9.2 and JMP 9 (SAS Institute Inc).

Results

Burden and Clinical Context of Id-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 atrial septal defect), 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 more than moderate, and TR with left ventricular systolic dysfunction (ejection fraction $<50\%$). Remaining patients had FTR-classified PHTN-linked with SPAP $\geq 50$mm Hg or Id-FTR with SPAP $<50$mm Hg. 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, Minn) or distantly referred ($P=0.35$). Clinical context, comparing Id-FTR versus PHTN-FTR versus traditional TR causes, showed Id-FTR associated with older age ($71.5\pm 13.8$ versus $67.4\pm 16.5$ versus $61.6\pm 20.8$ years respectively; $P<0.0001$-all comparisons), female sex (69.5% versus 71.0% and 54.7% respectively; $P<0.0001$) and AFib at diagnosis (51.0% versus 19.1% versus 11.5%; $P<0.0001$). AFib prevalence was higher in Id-FTR whether TR was severe (ERO $\geq 40$ mm$^2$, 57.3% versus 23.0% versus 14.8%; $P<0.0001$) or less severe (ERO $<40$ mm$^2$, 38.4% versus 16.0% versus 7.2%; $P<0.0001$). Thus, Id-FTR links to aging, and AFib underscores the importance of appropriate matching versus 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 had identical AFib prevalence and differed essentially by FTR degree. Observer variability was low for all measurements (all $P>0.23$) with all CCC $\geq 0.70$.

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 versus
Id-FTR, owing 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 versus 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 FS and increased RIMP versus controls-TTR, despite similar SPAP, demonstrating serious RV function alterations. Conversely, in PHTN-FTR, variables measuring RV function are discordant, with RV FS 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 versus controls-TTR demonstrates RA distention linked to FTR beyond the similarly prevalent AFib. FTR types were stratified according to FTR severity (ERO \( \geq 40 \text{mm}^2 \)) in Table 3. With severe FTR, RV enlarged in both groups, but RV FS declined in Id-FTR versus 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 versus Id-FTR).

### Table 1. Baseline Characteristics of Patients Overall and Stratified by Functional Tricuspid Regurgitation Type

<table>
<thead>
<tr>
<th>Group Characteristics</th>
<th>All Patients</th>
<th>Controls-TTR (N=99)</th>
<th>Id-FTR (N=141)</th>
<th>PHTN-FTR (N=140)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.2±14.0</td>
<td>72.2±12.3</td>
<td>71.4±13.9</td>
<td>70.4±15.3</td>
<td>0.62</td>
</tr>
<tr>
<td>AFib, (%)</td>
<td>46.1</td>
<td>49.5</td>
<td>51.0</td>
<td>39.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Sex, (%) males</td>
<td>31.3</td>
<td>32.3</td>
<td>31.2</td>
<td>30.7</td>
<td>0.96</td>
</tr>
<tr>
<td>EF, %</td>
<td>63.5±6.0</td>
<td>64.1±5.7</td>
<td>63.1±6.4</td>
<td>63.3±5.8</td>
<td>0.48</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>126.2±21.6</td>
<td>126.3±21.8</td>
<td>128.5±20.0</td>
<td>124.2±19.9</td>
<td>0.2</td>
</tr>
<tr>
<td>HR</td>
<td>72.7±16.0</td>
<td>73.9±16.3</td>
<td>71.4±17.2</td>
<td>73.3±14.2</td>
<td>0.43</td>
</tr>
<tr>
<td>CI L · min(^{-1}) · m(^2)</td>
<td>2.8±1.3</td>
<td>2.9±0.7</td>
<td>2.7±0.62</td>
<td>3.0±1.9</td>
<td>0.17</td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td>49.5±21.7</td>
<td>32.5±6.5</td>
<td>39.6±6.9</td>
<td>71.5±20.6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

TR indicates trivial (physiological) tricuspid regurgitation; Id-FTR, idiopathic functional TR; PHTN-FTR, functional TR due to pulmonary hypertension; AFib, atrial fibrillation; EF, ejection fraction; SBP, systolic blood pressure; HR, heart rate; CI, cardiac index; SPAP, systolic pulmonary artery pressure.

*\( P<0.05 \) vs Controls-TTR.
†\( P<0.001 \) vs Controls-TTR + \( P<0.05 \) vs Id-FTR.
‡\( P<0.0001 \) vs Id-FTR.

### Table 2. Characteristics of Tricuspid Regurgitation and Right Ventricle Stratified by Functional Tricuspid Regurgitation Type

<table>
<thead>
<tr>
<th>Etiologic Groups of Functional TR (FTR)</th>
<th>Controls-TTR</th>
<th>Id-FTR</th>
<th>PHTN-FTR</th>
<th>( P ) Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>141</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>TR Velocity, m/s</td>
<td>2.54±0.3</td>
<td>2.68±0.3</td>
<td>3.73±0.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>TR Duration, msec</td>
<td>397.2±55.8</td>
<td>407.6±50.8</td>
<td>422.0±50.2</td>
<td>0.001</td>
</tr>
<tr>
<td>TR ERO, mm(^2)</td>
<td>0</td>
<td>47±33†</td>
<td>44±20†</td>
<td>0.0001</td>
</tr>
<tr>
<td>TR RVol, mL/beat</td>
<td>0</td>
<td>37.0±19.5</td>
<td>51.3±25.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>TR jet area, cm(^2)</td>
<td>&lt;1.0</td>
<td>8.4±4.6†</td>
<td>13.9±6.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>TR jet/RA area ratio, %</td>
<td>&lt;5.0</td>
<td>41.19†</td>
<td>47.18§</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV-EDA index, cm(^2)/m(^2)</td>
<td>12.2±2.6</td>
<td>15.4±4.5†</td>
<td>16.8±6.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV-ESA index, cm(^2)/m(^2)</td>
<td>6.9±1.6</td>
<td>9.6±3.4†</td>
<td>9.8±5.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV-AFS, %</td>
<td>41.9±10.6</td>
<td>37.5±10.9</td>
<td>42.1±12.5</td>
<td>0.001</td>
</tr>
<tr>
<td>RIMP ratio</td>
<td>0.31±0.16</td>
<td>0.42±0.18†</td>
<td>0.47±0.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>RA volume index, mL/m(^2)</td>
<td>26.2±8.8</td>
<td>46.7±23.8</td>
<td>50.3±27.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

TT indicates trivial tricuspid regurgitation; Id-FTR, idiopathic functional tricuspid regurgitation; PHTN-FTR, pulmonary hypertension-related functional tricuspid regurgitation; ERO, effective regurgitant orifice; RVol, regurgitant volume; RA, right atrium; RV, right ventricle; 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></th>
<th>Control-TTR (N=99)</th>
<th>ERO &lt;40mm² (N=78)</th>
<th>ERO ≥40mm² (N=63)</th>
<th>P Value for trend</th>
<th>ERO &lt;40mm² (N=74)</th>
<th>ERO ≥40mm² (N=66)</th>
<th>P Value for trend</th>
<th>P Value 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>
<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>
<td>0.11</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>
<td>0.8</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>
<td>0.11</td>
</tr>
<tr>
<td>RV-AFS, %</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>
<td>0.0002</td>
</tr>
<tr>
<td>RA volume index, cm³/m²</td>
<td>26.2±8.8</td>
<td>38.1±17.9</td>
<td>57.5±25.8</td>
<td>&lt;0.0001</td>
<td>47.3±29.5</td>
<td>53.6±24.2</td>
<td>&lt;0.0001</td>
<td>0.6</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>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tenting height, cm</td>
<td>0.35±0.1</td>
<td>0.42±0.44</td>
<td>0.41±0.4</td>
<td>0.25</td>
<td>0.7±0.23</td>
<td>0.89±0.32</td>
<td>&lt;0.0001</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>
<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>3.74±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>
<td>0.0002</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>
<td>0.002</td>
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<tr>
<td>Leaflet length index, cm²</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>
<td>0.04</td>
</tr>
<tr>
<td>Leaflet/annular ratio</td>
<td>1.45±0.2</td>
<td>1.1±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>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV basal diameter index cm²/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>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV mid cavity 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>
<td>0.6</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>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV0, 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>
<td>0.5</td>
</tr>
<tr>
<td>RV wall thickness index mm²/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>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basal/ Mid cavity 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>
<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>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

RV indicates right ventricle; RA, right atrium; TR, tricuspid regurgitation; TTR indicates 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; RV-EDA, right ventricular end diastolic area; RV-ESA, right ventricular end systolic areas (4-chamber view); RV-AFS, right ventricular area fractional shortening; RIMP, right index of myocardial performance.

*P value for difference in trend between PHTN-FTR and Id-FTR.
†RV mid diameter and length product divided by basal diameter.

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/annulus ratio in Id-FTR (P<0.0001; AUC, 0.90) and higher tenting height in PHTN-FTR.

Figure 2. Valvular alterations in patients with Functional Tricuspid Regurgitation (FTR) according to FTR type, idiopathic (Id-FTR) versus related to pulmonary hypertension (PHTN-FTR). The variables represented are tricuspid annular diameter (2A), tricuspid valve tenting height (2B) and the ratio of tricuspid leaflet length to annular diameter (2C). 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 similar poor coaptation.
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 versus controls-TTR but was markedly increased in PHTN-FTR (Figure 4C), 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 4B and 4A). Thus, ratio of RV basal diameter to length (Figure 4E) and ratio of RV basal to midventricle

![Figure 3. Right ventricular and atrial alterations in 2 patients with functional tricuspid regurgitation. LV indicates left ventricle; LA, left atrium; RV, right ventricle; and RA, right atrium. Figure 3A corresponds to a patient with idiopathic tricuspid regurgitation and Figure 3B corresponds to a 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 2 patients.](image)

![Figure 4. Right Ventricular (RV) alterations according to Functional Tricuspid Regurgitation (FTR) type, idiopathic (Id-FTR) versus related to pulmonary hypertension (PHTN-FTR). The variables are RV basal width (diameter), indexed to body surface area (4A), RV midcavitary width index (4B), RV length index (4C), RV wall thickness (4D), and RV ratio of basal width to length (4E). 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 versus PHTN-FTR.](image)
ular diameter (Table 3) are highest in Id-FTR, consistent with RV conical deformation (versus controls). Conversely, lowest ratio of RV basal to midventricular diameter and highest sphericity index in PHTN-FTR are consistent with RV elliptical/spherical deformation (versus controls). RV shape and size changes in PHTN-FTR and Id-FTR versus controls are schematically presented in 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 $\geq 0.6$ cm (AUC, 0.88) and higher RVol (both $P<0.001$). Conversely, in Id-FTR, higher RV basal/length ratio is the only RV characteristic independently linked to leaflet/annular ratio $<1.1$ ($P<0.0001$; AUC, 0.88). RV wall thickness was highest in PHTN-FTR (Figure 4D), 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-etiology, 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 owing to marked annular enlargement, but valvular tenting plays no or minimal role. PHTN-FTR main mechanism is valvular tethering with tenting above the 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

Figure 5. Schematic representation of right ventricular (RV) and right atrial (RA) remodeling and valvular deformation comparing matched normal controls to idiopathic FTR (Id-FTR) versus related to pulmonary hypertension (PHTN-FTR). In Id-FTR and PHTN-FTR, for similar effective regurgitant orifice, similar systolic RV and RA enlargement versus 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.
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, seriously impact 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 links 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. Address to 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 1 entity, with annular dilatation as core mechanism, and a possible, but uncertain, contributing role of leaflet-tethering. RV remodeling contribution to FTR development is also controversial. 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 because substantial redundancy of leaflet tissue prevents TR in normal tricuspid valves (ratio leaflets/annular length, 1.45). With severe Id-FTR (ERO ≥0.4 cm²), leaflet coverage declined markedly, with decreasing coaptation not owing to retracted leaflets, as available valvular tissue was similar in all subsets. The Id-FTR entity is not well-known, not only mechanically but also clinically, and awareness of its existence was raised by few seminal reports. Although 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, 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, 3 underwent RA and atrioventricular groove biopsy, showing interstitial fibrosis with mild myocyte hypertrophy. These nonspecific observations incite further tissue analysis of tricuspid annulus to uncover biological mechanisms of Id-FTR.

Conversely, in PHTN-FTR, annular dilatation, although 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. PHTN-FTR, leaflet deformation with increased tenting height and intraventricular leaflets’ displacement, preventing appropriate coaptation, is the main determinant of ERO. Thus, our quantitative data show that Id-FTR and PHTN-FTR result from 2 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 versus controls-TTR; however, despite similar regurgitant lesion (ERO) by design, patients with PHTN-FTR versus Id-FTR incur larger RVol, owing 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 FS 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, although 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 versus 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, owing to afterload...
Thus, exact boundaries of Id-FTR definition do not affect unlikely PHTN (SPAP is the basis of clinical guidelines.4 If Id-FTR focused only on unlikely PHTN (SPAP ≤36 mm Hg), 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 id-FTR represents a notable proportion, may be severe, and is strongly associated to aging and Afib. Comprehensive quantitation also shows that FTR is a complex entity with contrasting mechanisms, depending on FTR type. Id-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/spherical deformation. Hence, RV remodeling and functional response to volume/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


**CLINICAL PERSPECTIVE**

Tricuspid regurgitation is frequent but not well-understood. Most often, it occurs despite structurally normal leaflets and is termed functional tricuspid regurgitation (FTR). This study evaluated the clinical context and mechanisms of FTR in patients in whom we performed quantification of tricuspid regurgitation, valvular deformation, and ventricular remodeling. We compared 2 FTR types that were caused by pulmonary hypertension versus FTR without overt cause (id-FTR). We matched groups for important characteristics at diagnosis (particularly the regurgitant orifice) and also included, as controls, patients of the same age with trivial TR. The results show that id-FTR occurs in older patients mostly with Afib. This observation is important because our study shows the mechanism of idiopathic FTR to be isolated enlargement of the tricuspid annulus, a known consequence of Afib, resulting in insufficient annulus coverage by the leaflets. This annular enlargement is associated with a conical deformation of the RV, which does not cause leaflet deformation. Conversely, with pulmonary hypertension, the RV is elongated and spherically deformed, leading to leaflet traction exerted by the papillary muscles, as well as deformation and tenting of leaflets, which cannot cover the annulus, despite its modest dilatation. Thus, the mechanism of FTR is not uniform. Our results enhance the understanding of the context and mechanisms for FTR and may help inform improved treatment strategies.
Clinical Context and Mechanism of Functional Tricuspid Regurgitation in Patients With and Without Pulmonary Hypertension

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