Valvular Heart Disease

Leaflet Area as a Determinant of Tricuspid Regurgitation Severity in Patients With Pulmonary Hypertension

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Background—Tricuspid regurgitation (TR) is a risk factor for mortality in pulmonary hypertension (PH). TR severity varies among patients with comparable degrees of PH and right ventricular remodeling. The contribution of leaflet adaptation to the pathophysiology of TR has yet to be examined. We hypothesized that tricuspid leaflet area (TLA) is increased in PH, and that the adequacy of this increase relative to right ventricular remodeling determines TR severity.

Methods and Results—A prospective cohort of 255 patients with PH from pre and postcapillary pathogeneses was assembled from 2 centers. Patients underwent a 3-dimensional echocardiogram focused on the tricuspid apparatus. TLA was measured with the Omni 4D software package. Compared with normal controls, patients with PH had a 2-fold increase in right ventricular volumes, 62% increase in annular area, and 49% increase in TLA. Those with severe TR demonstrated inadequate increase in TLA relative to the closure area, such that the ratio of TLA:closure area <1.78 was highly predictive of severe TR (odds ratio, 68.7; 95% confidence interval, 16.2–292.7). The median vena contracta width was 8.5 mm in the group with small TLA and large closure area as opposed to 4.8 mm in the group with large TLA and large closure area.

Conclusions—TLA plays a significant role in determining which patients with PH develop severe functional TR. The ratio of TLA:closure area, reflecting the balance between leaflet adaptation versus annular dilation and tethering forces, is an indicator of TR severity that may identify which patients stand to benefit from leaflet augmentation during tricuspid valve repair. (Circ Cardiovasc Imaging. 2015;8:e002714. DOI: 10.1161/CIRCIMAGING.114.002714.)

Key Words: echocardiography ■ pulmonary hypertension ■ tricuspid regurgitation

Severe tricuspid regurgitation (TR) develops in 10% to 30% of patients with pulmonary hypertension (PH) and presages death in 1 of 3 such patients within 1 year.1–3 Predicting and averting the development of severe TR is problematic because there is substantial variability in who develops severe TR, even after adjusting for pulmonary artery pressure and size of the tricuspid annulus and right ventricle (RV). This uncertainty has been attributed, in part, to an incomplete understanding of the pathophysiology at hand.4

See Clinical Perspective

Functional TR, which represents 90% of cases,5 results from geometric distortions in any of 4 inter-related components, such as (1) tricuspid valve leaflets, (2) tricuspid annulus, (3) papillary muscles and chordae, and (4) RV size and shape, including the interventricular septum and left ventricular interactions. To date, the emphasis has primarily been on tricuspid annular dilation, and secondarily on RV remodeling with papillary muscle displacement leading to valvular tethering.6

The contribution of the tricuspid leaflets to the pathophysiology of functional TR has largely been neglected, perhaps owing to the concept that the leaflets should be normal in functional valvulopathies, or to inherent challenges in quantitatively measuring leaflet tissue. In previous work, our group developed and validated a technique to measure mitral leaflet area and demonstrated that ventricular dilation was accompanied by mitral leaflet growth so that mitral regurgitation developed when leaflet growth was inadequate to cover the valve closure area.7

By defining the 3-dimensional (3D) changes in leaflet, annular, ventricular, and tethering geometry using our previously validated approach, the objective of this study was...
to determine whether tricuspid leaflet area (TLA) was correlated with functional TR in a cohort of patients with PH. We hypothesized that TLA is increased in PH, and that its adequacy relative to RV remodeling is a strong determinant of TR severity.

This hypothesis, if correct, would provide the justification and context to investigate the mechanisms of leaflet adaptation and the use of leaflet augmentation as a therapeutic procedure for functional TR, which is currently a topic of ongoing debate. Although not yet proven, patients with inadequate leaflet adaptation would be expected to benefit more from leaflet augmentation. Echocardiographic research has been instrumental in guiding therapy for TR, leading to (1) a redesigned tricuspid annuloplasty ring that mimics the natural 3D saddle-shape of the annulus (MC3, Edwards, Irvine, CA), (2) guideline recommendations to repair functional TR if the mid-diastole of the annulus exceed 40 mm, and in some centers, (3) an adopted practice to perform leaflet augmentation if the tenting distance exceeds 8 mm.

Methods

Study Design

A prospective 2-center cohort of patients with PH was assembled. Patients underwent a standardized 2D and 3D echocardiographic assessment, with a specific focus on the right heart and tricuspid valve. The dependent variable was severity of TR quantified according to the vena contracta (VC) width. TLA was measured offline using the Omni 4D software package. The independent variable of interest was the ratio of TLA divided by tricuspid closure area, which reflects the adaptation (ie, growth) of the valve leaflets to cover the distended and tented systolic closure area and thus maintain valvular competency. Each center’s institutional review committee approved the study and patients provided informed consent to be included.

Setting

Patients were identified and recruited from the PH programs at the Massachusetts General Hospital (Boston, MA) and Hammersmith Hospital (London, United Kingdom), both of which are tertiary referral centers for PH. Recruitment at the Massachusetts General Hospital occurred between May 2012 and March 2013. Recruitment at the Hammersmith Hospital occurred between January 2012 and April 2013. Echocardiograms were performed and analyzed in the cardiac ultrasound facilities of the respective hospitals, using the Philips IE33 machine and Xcelera/QLAB workstation (Philips Medical Systems, Andover, MA) at the former, and the GE Vivid 7 machine and EchoPAC workstation (GE, Milwaukee, WI) at the latter.

Participants

Inclusion criteria were (1) TR velocity ≥3.5 m/s, corresponding to an estimated pulmonary artery systolic pressure (PASP) of ≥50 mm Hg, (2) diagnosis of PH confirmed by a cardiologist or pulmonologist within the PH program. The majority of patients had undergone diagnostic right heart catheterization as part of their initial clinical investigations. Invasive PASP was not remeasured for the purposes of this study, therefore, noninvasive PASP was used to identify eligible patients, and those with insufficient TR jet signal to obtain a noninvasive PASP were excluded. Other exclusion criteria were atrial fibrillation at the time of the echocardiogram, inadequate image quality to visualize the right heart or tricuspid valve, pacemaker, and organic TR pathogenesis. All types of PH were eligible, including precapillary (pulmonary arterial hypertension and chronic thromboembolic PH) and postcapillary (PH due to left heart diseases). In addition, measurements of TLA and closure area were obtained in a group of 34 normal controls free of structural heart disease who were referred to the echocardiography laboratory.

Echocardiographic Protocol

A comprehensive echocardiogram was performed, with special attention to optimize the right heart acquisitions. The RV was imaged from multiple views, including but not limited to the RV inflow view, RV-focused and RV-modified apical 4-chamber views. The TR jet was imaged by color Doppler in the parasternal RV inflow view, parasternal short-axis view, apical 4-chamber view, and subcostal view. Two-dimensional measurements of RV size and function were made according to the American Society of Echocardiography guidelines for the echocardiographic assessment of the right heart. All measurements were made at end-expiration.

The 3D echocardiographic protocol consisted of 4-beat full volume acquisitions in the RV-focused apical 4-chamber view and the parasternal RV inflow view, and in a subset of patients, 6-beat full volume color Doppler acquisitions in the same 2 views. A single-beat 3D zoom was also obtained. The sector depth, sector width, and elevation width were adjusted to focus on the tricuspid valve leaflets throughout the cardiac cycle. For full volume color Doppler acquisitions, a minimum frame rate of 12 per second was required; the number of beats in the full volume acquisition could be increased to obtain a higher frame rate if the R–R intervals were regular. QLAB’s multiplane reconstruction (Philips Medical Systems) was used to measure VC area, and TomTec’s 4D RV Function (TomTec, Munich, Germany) was used to measure RV volumes.

Measurement of TR Severity

The VC width was measured in duplicate or triplicate (ie, in 2–3 successive beats) with held end-expiration from the apical 4-chamber and parasternal RV inflow views. To account for the possibility of nonsymmetrical orifices, biplane VC width was calculated by averaging the VC widths from these 2 roughly orthogonal views. This biplane VC approach has been validated in mitral regurgitation and shown to be closely correlated with regurgitant volume for both circular and elliptical orifices. VC width was preserved as a continuous variable, with the exception of descriptive comparisons for which TR by VC width was grouped as mild (<4 mm), moderate (4–7 mm), or severe (≥7 mm). The echocardiography specialist’s (all level III trained) semiquantitative assessment of TR severity based on color Doppler jet appearance and hepatic vein reversal was also abstracted from the clinical report. Finally, TR was assessed by 3D VC area in a subset of 33 patients during the latter part of the study when a routine full volume color Doppler acquisition was added to the echocardiographic protocol.

Three-dimensional VC area was measured as follows: the 3D full volume color Doppler data set was opened in the multiplanar reconstruction application, the 2 orthogonal long-axis planes were aligned parallel to the direction of the proximal TR jet, the short-axis plane was aligned perpendicular to the VC (the narrowest neck of the proximal TR jet just below the flow convergence zone), and the resulting short-axis image of the VC was traced to yield VC area. As for the measurements of 2D VC width, the measurements of 3D VC area were repeated and averaged in 2 to 3 beats and in both the apical and parasternal datasets.

Measurement of TLA

The 3D full volume data set was imported into the Omni 4D software package (M.D.H.). The open tricuspid leaflets were traced in mid-diastole on successive rotational long-axis planes and reconstructed to obtain the TLA, as previously validated on the mitral valve (because leaflet tissue overlaps at the coaptation point, tracing in systole is less accurate, and is affected by systolic leaflet stretch). The tricuspid closure area was traced in midsystole as the
leaflet area separating the RV and right atrium necessary to occlude the tricuspid orifice, as required by annular and ventricular tethering. The tricuspid annular area (projected onto its least-squares plane) was also traced in midsystole. The ratio of TLA divided by tricuspid closure area was the primary predictor variable. A reduction in this ratio represents small valve leaflets relative to a large annulus and tented closure area, leading to valvular insufficiency. The observers underwent training sessions for the Omni 4D software at the study onset and were blinded to the TR severity parameters when making leaflet measurements to ensure accuracy.

Table 1. Clinical Characteristics of Patients With Pulmonary Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Severe TR (n=53)</th>
<th>Nonsevere TR (n=202)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (Q1, Q3)</td>
<td>45.0 (34.0, 58.0)</td>
<td>43.0 (37.0, 52.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Female sex</td>
<td>17 (32.1)</td>
<td>74 (36.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (11.3)</td>
<td>12 (5.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (24.5)</td>
<td>43 (21.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6 (10.3)</td>
<td>11 (5.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5 (9.4)</td>
<td>16 (7.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>NYHA III–IV</td>
<td>45 (84.9)</td>
<td>149 (73.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>PH pathogenesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precapillary</td>
<td>33 (62.3)</td>
<td>101 (50.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Postcapillary</td>
<td>20 (37.7)</td>
<td>101 (50.0)</td>
<td></td>
</tr>
<tr>
<td>PH therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7 (13.2)</td>
<td>22 (10.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>15 (28.3)</td>
<td>51 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Endothelin antagonist</td>
<td>15 (28.3)</td>
<td>79 (39.1)</td>
<td></td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>16 (30.2)</td>
<td>50 (24.8)</td>
<td></td>
</tr>
</tbody>
</table>

N (%) unless otherwise specified. Severe TR defined as vena contracta width ≥7 mm, nonsevere TR defined as <7 mm. NYHA indicates New York Heart Association; PDE5, phosphodiesterase-5; Q1, quartile 1; Q3, quartile 3; and TR, tricuspid regurgitation.

Table 2. Echocardiographic Parameters of Patients With Pulmonary Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Severe TR (n=53)</th>
<th>Nonsevere TR (n=202)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-dimensional vena contracta width, mm</td>
<td>9.0 (8.4, 9.8)</td>
<td>3.4 (2.7, 5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3-dimensional vena contracta area, cm²</td>
<td>0.67 (0.59, 0.85)</td>
<td>0.28 (0.20, 0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>79.0 (69.0, 94.0)</td>
<td>80.0 (64.8, 94.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>RA volume, mL</td>
<td>183.5 (132.5, 220.0)</td>
<td>135.0 (98.0, 187.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>RV end-diastolic volume, mL</td>
<td>205.0 (189.0, 256.0)</td>
<td>187.0 (152.0, 218.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>RV end-systolic volume, mL</td>
<td>146.0 (123.0, 189.0)</td>
<td>122.0 (89.5, 166.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV stroke volume, mL</td>
<td>57.5 (50.0, 69.0)</td>
<td>57.0 (435, 72.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>27.5 (23.0, 34.5)</td>
<td>32.0 (23.0, 41.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>48.0 (33.0, 64.0)</td>
<td>68.5 (62.0, 74.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Leaflet area, cm²</td>
<td>20.6 (18.9, 23.1)</td>
<td>21.8 (18.4, 25.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Closure area, cm²</td>
<td>15.6 (13.5, 16.8)</td>
<td>10.9 (9.8, 12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Annulus area, cm²</td>
<td>15.8 (13.2, 16.8)</td>
<td>10.8 (9.4, 12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leaflet area:closure area ratio</td>
<td>1.34 (1.22, 1.56)</td>
<td>1.98 (1.78, 2.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leaflet area:annular area ratio</td>
<td>1.36 (1.24, 1.60)</td>
<td>2.04 (1.70, 2.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tenting volume, cm³</td>
<td>3.2 (2.9, 3.4)</td>
<td>1.9 (1.5, 2.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Median (Q1, Q3). Severe TR defined as vena contracta width ≥7 mm, nonsevere TR defined as <7 mm. LA indicates left atrium; LV, left ventricle; PASP, pulmonary artery systolic pressure; Q1, quartile 1; Q3, quartile 3; RA, right atrium; RV, right ventricle; and TR, tricuspid regurgitation.
and prevent bias. Leaflet measurements were made by a second independent observer in a random subset of patients to calculate the interrater reliability.

Statistical Methods
Continuous variables were presented as medians with their 25th percentile (Q1) and 75th percentile (Q3). Nonparametric Wilcoxon rank-sum tests and Spearman correlations were used for univariate analysis. Linear regression was used for multivariable analysis, testing the hypothesis that the ratio of TLA:closure area would be inversely related to the TR VC (log transformed because of skewed distribution) after adjusting for covariates. A receiver-operating characteristics curve was also constructed to identify the optimal cutoff for the ratio of TLA:closure area to predict severe TR. No previous studies on TLA were available to guide sample size calculation; however, our previous studies on mitral leaflet adaptation were adequately powered with samples sizes of 80 to 90 patients\(^7,18\) such that the projected recruitment of 250 patients over a 1-year span was expected to be sufficient to test this hypothesis. All analyses were performed with the STATA 13 statistical software package (College Station, TX).

Results
The cohort consisted of 164 men and 91 women with a median age of 43.0 years (Q1, 36.0; Q3, 53.0). The median PASP was 79.0 mmHg (Q1, 65.8; Q3, 94.6) and the pathogenesis of PH was evenly distributed between precapillary (n=134, 52.5%) and postcapillary causes (n=121, 47.5%). Baseline characteristics stratified by severe versus nonsevere TR are shown in Table 1.

TR severity classified according to the VC width was mild in 116 (45.5%) patients, moderate in 86 (33.7%) patients, and severe in 53 (20.8%) patients. The distribution was internally consistent with the clinical echocardiographer’s report that was mild in 130 (51.0%) patients, moderate in 76 (29.8%) patients, and severe in 49 (19.2%) patients. Echocardiographic parameters stratified by severity of TR are shown in Table 2.

Patients with severe TR were more likely to have increased right atrial volume, increased RV volume, decreased RV and LV ejection fractions (despite a similar proportion of postcapillary PH pathogenesis). The median PASP did not vary according to the severity of TR.

![Figure 1](http://circimaging.ahajournals.org/)

**Figure 1.** Tricuspid leaflet area (TLA), annulus area, and tenting volume in 3 groups. Compared with healthy controls, patients with pulmonary hypertension (PH) had greater median TLA, annulus area, and tenting volume. Although TLA was similar in PH patients with severe tricuspid regurgitation (TR) and nonsevere TR, annulus area was significantly larger in those with severe TR such that the TLA was insufficient to maintain valvular competency. Sensitivity analysis showed that these results were not unduly influenced by outlier values.

![Figure 2](http://circimaging.ahajournals.org/)

**Figure 2.** Leaflet area:closure area ratio was inversely correlated with tricuspid regurgitation severity as measured by vena contracta width ($R=-0.66$; $P<0.0001$).

![Figure 3](http://circimaging.ahajournals.org/)

**Figure 3.** Leaflet area:closure area ratio discriminated between pulmonary hypertension patients with vs without severe TR (area under ROC curve of 0.9206, optimal cutoff value of 1.78).

![Figure 4](http://circimaging.ahajournals.org/)

**Figure 4.** Tricuspid regurgitation (TR) severity as a function of tricuspid leaflet area (TLA) and closure area greater than or less than median. Pulmonary hypertension patients with large TLA and small closure area had the least TR (far left), whereas those with small TLA and large closure area had the most TR (far right).
Compared with healthy controls, patients with PH had a 112% increase in RV end-diastolic volume (median, 190.0 mL versus 89.5 mL; \(P<0.001\)), a 62% increase in tricuspid annular area (median, 11.2 cm\(^2\) versus 6.9 cm\(^2\); \(P<0.001\)), and a 49% increase in TLA (median, 21.4 cm\(^2\) versus 14.4 cm\(^2\); \(P<0.001\)). Those with PH and severe TR had an incremental increase in RV volumes, annulus area, and tenting volume (Figure 1).

Despite the increase in RV volume and annulus area in patients with worsening TR, there was a slight decrease in TLA from 22.5 cm\(^2\) in patients with mild TR to 20.6 cm\(^2\) in patients with severe TR. The ratio of TLA:closure area was inversely correlated with the VC width (Figure 2). Specifically, the ratio of TLA:closure area was 2.09, 1.87, and 1.34 in patients with mild, moderate, and severe TR, respectively (Spearman R, \(-0.66\); \(P<0.0001\)). The area under the receiver-operating characteristics curve was 0.93 for the ratio of TLA:closure area to predict severe TR, and the optimal cutoff for this ratio was <1.78 (odds ratio, 68.7; 95% confidence interval (CI), 16.2, 292.7; Figure 3).

To further define the interplay between closure area and TLA, patients were divided into 4 groups based on the presence of large versus small (greater than versus less than median) closure area and TLA (Figure 4). Patients with large closure area (>11.7 cm\(^2\)) and small TLA (<21.4 cm\(^2\)) had a markedly greater likelihood of severe TR: median VC width was 8.5 mm in the large closure area–small TLA group (n=48), 4.8 mm in the large closure area–large TLA group (n=83), 3.3 mm in the small closure area–small TLA group (n=76), and 3.0 mm in the small closure area–large TLA group (n=48; Figure 5).

To determine the independent predictors of TR severity, multivariable linear regression was performed with log-transformed VC width as the dependent variable and the following covariates: TLA, closure area, tenting volume, RV end-diastolic volume, PASP, PH pathogenesis, age, and sex. As shown in Table 3, the independent predictors of greater TR severity were smaller TLA (coefficient, \(-0.028\); 95% CI, \(-0.041\) to \(-0.014\)), larger closure area (coefficient, 0.088; 95% CI, 0.055–0.120), larger tenting volume (coefficient, 0.298; 95% CI, 0.207–0.390), and precapillary pathogenesis (coefficient, 0.100; 95% CI, 0.038–0.162).

In the subset of patients with available 3D VC area, there was a strong correlation between 2D VC width and 3D VC area (Spearman R=0.75; \(P<0.001\)). Severe TR defined by 2D VC width  7 mm was discriminated with a high degree of accuracy by 3D VC area (c-statistic, 0.97). Adding treating center as a covariate in the multivariable model did not affect the results. Inter-rater reliability was shown by intraclass coefficients of 0.88 and 0.84 for TLA and closure area, respectively.

### Table 3. Linear Regression to Predict Tricuspid Regurgitation Vena Contracta (Log)

<table>
<thead>
<tr>
<th></th>
<th>Univariable Analysis</th>
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<th>Multivariable Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
<td>(P) Value</td>
<td>Coefficient</td>
<td>95% CI</td>
<td>(P) Value</td>
</tr>
<tr>
<td>Leaflet area, per cm(^2)</td>
<td>(-0.010)</td>
<td>((-0.025, 0.005))</td>
<td>0.18</td>
<td>(-0.036)</td>
<td>((-0.048, -0.024))</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Closure area, per cm(^2)</td>
<td>0.117</td>
<td>(0.097, 0.137)</td>
<td>&lt;0.001</td>
<td>0.116</td>
<td>(0.208, 0.389)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tenting volume, per cm(^3)</td>
<td>0.384</td>
<td>(0.314, 0.453)</td>
<td>&lt;0.001</td>
<td>0.298</td>
<td>(&lt;0.001, 0.000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV end-diastolic volume, per mL</td>
<td>0.002</td>
<td>(0.0004, 0.003)</td>
<td>0.01</td>
<td>-0.0003</td>
<td>(&lt;0.001, 0.003)</td>
<td>0.41</td>
</tr>
<tr>
<td>PASP, per mmHg</td>
<td>0.002</td>
<td>((-0.001, 0.005))</td>
<td>0.30</td>
<td>0.0008</td>
<td>((-0.219, -0.049))</td>
<td>0.42</td>
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<tr>
<td>Age, per y</td>
<td>(-0.001)</td>
<td>((-0.006, 0.003))</td>
<td>0.57</td>
<td>(-0.003)</td>
<td>(0.092, 0.141)</td>
<td>0.14</td>
</tr>
<tr>
<td>Female sex</td>
<td>(-0.030)</td>
<td>((-0.170, 0.111))</td>
<td>0.68</td>
<td>(-0.026)</td>
<td>((-0.006, 0.001))</td>
<td>0.57</td>
</tr>
<tr>
<td>Precapillary pathogenesis</td>
<td>0.315</td>
<td>(0.260, 0.370)</td>
<td>&lt;0.001</td>
<td>0.134</td>
<td>((-0.116, 0.064))</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PASP, pulmonary artery systolic pressure; and RV, right ventricle.
Discussion

Although previous studies have explored annular and subvalvular geometry as determinants of functional TR, this study now shows that TLA plays a significant role in the pathophysiology. In this prospective cohort of patients with PH, RV pressure overload and remodeling were associated with a 49% increase in TLA compared with healthy controls. When TLA was inadequate to cover the closure area, a graded increase in TR severity was observed. The ratio of TLA:closure area, reflecting the balance between leaflet adaptation versus annular dilation and tethering geometry, proved to be a strong indicator of functional TR severity.

The pathophysiology of functional TR has been an area of active research during the past 30 years, starting with the finding that annular dilation was a critical component in its development. Subsequently, it was found that valvular tethering played a major role in the development of functional TR. The factors leading to valvular tethering were reported in a series of studies: RV spherical remodeling, interventricular septal shift, left ventricular interactions, and RV papillary muscle displacement. This study has added a novel mechanistic component, TLA, to our understanding of the pathophysiology of functional TR.

The current finding is consistent with recent work on leaflet adaptation in functional mitral regurgitation. Compared with normal controls, patients with dilated cardiomyopathy or inferior wall motion abnormality had a 35% increase in mitral leaflet area. A ratio of mitral leaflet area:closure area <1.7 predicted significant valvular incompetence, similar to the ratio of <1.78 found in this series of TR. Patients with dilated left ventricles in the context of aortic regurgitation were also found to have a 31% increase in mitral leaflet area, albeit a preserved ratio of mitral leaflet area:closure area such that significant functional mitral regurgitation was rare. Interestingly, the biological mechanism for increased leaflet area was shown in a sheep model in which mechanical leaflet tethering/stress caused by papillary muscle retraction reactivated embryonic pathways for leaflet growth.

Beyond the mechanistic implications, our findings have clinical significance for repair of functional TR (most commonly performed for postcapillary PH pathogeneses). Despite contemporary practice of tricuspid valve repair with ring annuloplasty, the incidence of residual moderate-to-severe TR is 15% to 22% within the first month and up to 44% in long-term follow-up. Because ring annuloplasty only addresses 1 facet of the problem, annular dilation, it is not surprising to observe that other facets, such as RV spherical remodeling and left-sided dysfunction and their resultant tethering effects are the main predictors of recurrent TR. Our findings indicate that inadequate TLA relative to the demand for closure area imparted by tethering may be another important predictor of recurrent TR. Surgical RV reduction by plication of the lateral free wall has been used to address this issue at the subvalvular level in a case-series of 17 patients from Germany. Tricuspid leaflet augmentation by autologous pericardial patch at the time of tricuspid ring annuloplasty has been used by multiple groups and achieved recurrent TR rates as low as 2%. Newer patch materials using extracellular matrix scaffolds are also under development for this purpose.

Our approach to quantify TLA may be applied to identify which patients could derive the greatest benefit from a leaflet augmentation procedure.

Limitations and Future Directions

Total TLA was measured, not differential adaptation of individual leaflets. Clinically, however, leaflet augmentation procedures empirically achieve good results targeting the anterior leaflet and sometimes the anterior portion of the posterior leaflet, so this may not alter practice. The Omni 4D software package uniquely provides total open TLA independent of systolic stretch; commercial vendors have developed similar products to measure closed leaflet parameters (eg, QLAB MVQ, Philips Medical Systems), and could in principle provide open area as well. TR severity was measured at a single point in time; longitudinal progression in TR severity as a function of leaflet adaptation would be of interest in future studies. VC width may vary when the orifice shape is elliptical; to minimize the potential error of using single-plane VC width, biplane VC was measured in orthogonal views, and furthermore, validated against 3D VC area. Finally, there is significant inherent variability in tricuspid valve anatomy, including but not limited to the leaflets and subvalvular apparatus, such that the mechanism of functional TR is often multifactorial and difficult to predict.

In conclusion, TLA is an important contributor to the development of functional TR. Strengths of this study include a prospective 2-center design, measurement of 3D leaflet area using a specialized software tool which has been validated against explanted valves and computed tomography, and gradation of TR severity according to VC, which has been shown to be more accurate and reproducible compared with jet area or visual assessment and the most prognostic indicator of TR severity. By integrating TLA with annular area and tenting volume, a more complete understanding of the pathophysiology of functional TR is obtained. Fundamentally, this is represented by a simple ratio of TLA:closure area, in which closure area reflects both annular area and tenting. Future studies may advance the use of these leaflet parameters by demonstrating their ability to select patients in need of patch augmentation or other ancillary procedures at the time of tricuspid valve ring annuloplasty, and correlating the observed changes in TLA with the biological pathways responsible for leaflet proliferation.

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Disclosures

Dr Rudski reports minor holding of GE stock outside of a managed portfolio.

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**CLINICAL PERSPECTIVE**

The development of severe tricuspid regurgitation heralds a poor prognosis in patients with pulmonary hypertension. However, there is limited information about the role of the tricuspid leaflets in the pathophysiology and treatment of this complication. We evaluated the contribution of tricuspid leaflet adaptation in 255 patients from 2 centers. We hypothesized that tricuspid regurgitation severity would be inversely correlated to tricuspid leaflet area measured by 3-dimensional echocardiography. Compared with healthy controls, tricuspid leaflet area was 49% larger in patients with pulmonary hypertension. The ratio of total tricuspid leaflet area:closure area, reflecting the adequacy of tricuspid leaflet adaptation relative to right ventricular and annular remodeling, was highly associated with the severity of functional tricuspid regurgitation. Patients with small leaflet area and large closure area had the highest risk of manifesting severe tricuspid regurgitation, whereas those with large leaflet area and small closure area had the lowest risk. Beyond the mechanistic implications, our findings underscore the potential use of tricuspid leaflet augmentation procedures performed at the time of tricuspid valve repair surgery in selected patients who have insufficient tricuspid leaflet tissue to maintain valvar competency in the face of ventricular remodeling and annular dilation. This will have to be tested in prospective trials.
Leaflet Area as a Determinant of Tricuspid Regurgitation Severity in Patients With Pulmonary Hypertension

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