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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1161/CIRCIMAGING.114.002714</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:29048898">http://nrs.harvard.edu/urn-3:HUL.InstRepos:29048898</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Open Access Policy Articles, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP</a></td>
</tr>
</tbody>
</table>
Leaflet Area as a Determinant of Tricuspid Regurgitation Severity in Patients with Pulmonary Hypertension

Jonathan Afilalo, MD, MSc1,5, Julia Grapsa, MD2, Petros Nihoyannopoulos, MD2, Jonathan Beaudoin, MD5, J. Simon R. Gibbs, MD3, Richard N. Channick, MD4, David Langleben, MD1, Lawrence G. Rudski, MD1, Lanqi Hua, RDCS5, Mark D. Handschumacher, BS5, Michael H. Picard, MD5, and Robert A. Levine, MD5

1Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Canada
2Cardiac Ultrasound Laboratory, Division of Cardiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
3National Pulmonary Hypertension Service, Division of Cardiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
4Pulmonary Hypertension and Thromboendarterectomy Program, Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Harvard University, Boston, MA
5Cardiac Ultrasound Laboratory, Division of Cardiology, Massachusetts General Hospital, Harvard University, Boston, MA

Abstract

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 (RV) 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 its size relative to RV remodeling determines TR severity.

Methods and Results—A prospective cohort of 255 patients with PH from pre- and post-capillary etiologies was assembled from two centers. Patients underwent a 3-D echocardiogram focused on the tricuspid apparatus. TLA was measured with the Omni custom software package. Compared with normal controls, PH patients had a twofold increase in RV volumes, 62% increase in annulus 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-to-closure area <1.78 was highly predictive of severe TR (odds ratio 68.7; 95% CI 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-to-closure area, reflecting the balance between leaflet adaptation vs. 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.

Keywords
tricuspid regurgitation; pulmonary hypertension; echocardiography

Severe tricuspid regurgitation (TR) develops in 10-30% of patients with pulmonary hypertension (PH) and presages death in 1/3 such patients within one year\(^1\)-\(^3\). Predicting and averting the development of severe TR is problematic since 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\(^4\).

Functional TR, which represents 90% of cases\(^5\), results from geometric distortions in any of four inter-related components: (1) tricuspid valve leaflets, (2) tricuspid annulus, (3) papillary muscles and chordae, and (4) right ventricular size and shape, including the interventricular septum and left ventricular interactions. To date, the emphasis has primarily been on tricuspid annulus dilation, and secondarily on right ventricular remodeling with papillary muscle displacement leading to 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 prior 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-D changes in leaflet, annular, ventricular, and tethering geometry using our previously validated approach, the objective of this study was to determine whether tricuspid leaflet surface 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\(^8\) and the use of leaflet augmentation as a therapeutic procedure for functional TR, which is currently a topic of ongoing debate\(^9\). Although not yet proven, patients with inadequate leaflet adaptation would be expected to benefit more from leaflet augmentation. Echocardiographic research\(^10\) has been instrumental in guiding therapy for TR, leading to: (i) a redesigned tricuspid annuloplasty ring that mimics the natural 3-dimensional saddle-shape of the annulus (MC3, Edwards, Irvine, CA), (ii) guideline recommendations to repair functional TR if the annular dilation exceeds 40 mm\(^11\),\(^12\), and in some centers, (iii) an adopted practice to perform leaflet augmentation if the tenting distance exceeds 8 mm\(^13\),\(^14\).
Methods

Study Design

A prospective two-center cohort of patients with PH was assembled. Patients underwent a standardized 2-D and 3-D 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 \(^15\). TLA was measured offline using the Omni 4D custom software package. The independent variable of interest was the ratio of TLA divided by tricuspid closure area, which reflects the adaptation (i.e. 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 pulmonary hypertension programs at the Massachusetts General Hospital (Boston, MA) and Hammersmith Hospital (London, UK), both of which are tertiary referral centers for patients with 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 meters/second, 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 pulmonary hypertension program. The majority of patients had undergone diagnostic right heart catheterization as part of their initial clinical investigations. Invasive PASP was not re-measured 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 and/or tricuspid valve, pacemaker, and organic TR etiology. All types of PH were eligible, including pre-capillary (pulmonary arterial hypertension, chronic thromboembolic PH) and post-capillary (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 lab.

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. In each of these views, the color Doppler baseline was lowered to 28 ± 8 cm/s to optimize the VC appearance. 2-D measures 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 held end-expiration.

The 3-D 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 two views. A single-beat 3-D 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 multi-plane reconstruction (Philips Medical Systems, Andover, MA) was used to measure VC area, and TomTec’s 4-D RV Function (TomTec, Munich, Germany) was used to measure RV volumes.

**Measurement of TR Severity**

The VC width was measured in duplicate or triplicate (i.e. 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 two 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) semi-quantitative assessment of TR severity based on color Doppler jet appearance and hepatic vein reversal was also abstracted from the clinical report. Lastly, TR was assessed by 3-D 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.

3-D VC area was measured as follows: the 3-D full volume color Doppler dataset was opened in the multi-planar reconstruction application, the two 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 2-D VC width, the measurements of 3-D VC area were repeated and averaged in 2-3 successive beats and in both the apical and parasternal datasets.

**Measurement of TLA**

The 3-D full volume dataset was imported into the Omni custom software package. The open tricuspid leaflets were traced in mid-diastole in multiple planes and reconstructed to obtain the TLA, as previously validated on the mitral valve (due to overlap of leaflet tissue at the coaptation point, tracing in systole is less accurate, and is affected by systolic leaflet

*Circ Cardiovasc Imaging. Author manuscript; available in PMC 2016 May 01.*
The tricuspid closure area was traced in mid-systole as the leaflet area separating the RV and RA 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 mid-systole. 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 larger annulus and more tented closure area, leading to valvular insufficiency. The observers underwent training sessions for the Omni software at the study onset and were blinded to the TR severity parameters when making leaflet measurements to ensure accuracy and prevent bias. Leaflet measurements were made by a second independent observer in a random subset of patients to calculate the intraclass coefficients (ICC).

**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 analyses. Linear regression was used for multivariable analysis, testing the primary hypothesis that the ratio of TLA-to-closure area would be inversely related to the TR VC (log transformed due to skewed distribution) after adjusting for covariates. A receiver operating characteristics (ROC) curve was also constructed to identify the optimal cutoff for the ratio of TLA-to-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 80-90 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 males and 91 females with a median age of 43.0 years (Q1 36.0, Q3 53.0). The median PASP was 79.0 mm Hg (Q1 65.8, Q3 94.6) and the etiology of PH was evenly distributed between pre-capillary (N=134, 52.5%) and post-capillary causes (N=121, 47.5%). Baseline characteristics stratified by severe vs. non-severe TR are shown in Table 1.

TR severity classified according to the VC width was: mild in 116 (45.5%), moderate in 86 (33.7%), and severe in 53 (20.8%). The distribution was internally consistent with the clinical echocardiographer's report that was: mild in 130 (51.0%), moderate in 76 (29.8%), and severe in 49 (19.2%). 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 volumes, decreased RV and LV ejection fractions (despite a similar proportion of post-capillary PH etiology). The median PASP did not vary according to the severity of TR.

Compared with healthy controls, patients with PH had a 112% increase in RV enddiastolic volume (median 190.0 mL vs. 89.5 mL, \(P<0.001\)), a 62% increase in tricuspid annulus area (median 11.2 cm\(^2\) vs. 6.9 cm\(^2\), \(P<0.001\)), and a 49% increase in TLA (median 21.4 cm\(^2\) vs.
14.4 cm², 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 volumes and annulus area with worsening TR, there was a slight decrease in TLA from 22.5 cm² in patients with mild TR to 20.6 cm² in patients with severe TR. The ratio of TLA-to-closure area was inversely correlated with the VC width (Figure 2). Specifically, the ratio of TLA-to-closure area was 2.09, 1.87, and 1.34 in patients with mild, moderate, and severe TR, respectively (Spearman's R -0.66, P<0.0001). The area under the ROC curve was 0.93 for the ratio of TLA-to-closure area to predict severe TR, and the optimal cutoff for this ratio was <1.78 (OR 68.7, 95% 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 vs. small (> vs. < median) closure area and TLA (Figure 4). Patients with large closure area (>11.7 cm²) and small TLA (<21.4 cm²) 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 etiology, 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, -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 pre-capillary etiology (coefficient 0.100, 95% CI 0.038, 0.162).

In the subset of patients with available 3-D VC area, there was a strong correlation between 2-D VC width and 3-D VC area (Spearman R=0.75, P<0.001). Severe TR defined by 2-D VC width ≥7 mm was discriminated with a high degree of accuracy by 3-D 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 ICCs of 0.88 and 0.84 for tricuspid leaflet area and closure area, respectively.

**Discussion**

While 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 PH patients, RV pressure overload and remodeling was 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-to-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 over the past 30 years, starting with the finding that annular dilatation was a critical component in its
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; however, they often had a greater relative increase in closure area, such that functional mitral regurgitation developed. A ratio of mitral leaflet area to 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 to closure area such that significant functional mitral regurgitation was very 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 post-capillary PH etiologies). Despite contemporary practice of tricuspid valve repair with ring annuloplasty, the incidence of residual moderate-to-severe TR is 15-22% within the first month, and up to 44% in long-term follow-up. Since ring annuloplasty only addresses one 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 significantly 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 leaflet area 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 custom software package uniquely provides total open TLA independent of systolic stretch; commercial vendors have developed similar products to measure closed leaflet parameters (e.g. QLAB MVQ, Philips Medical Systems, Andover, MA), 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\textsuperscript{33}; to minimize the potential error of using single-plane VC width, biplane VC was measured in orthogonal views\textsuperscript{17}, and furthermore, validated against 3-D VC area. Lastly, 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 two-center design, measurement of 3-D leaflet area using a specialized software tool which has been validated against explanted valves\textsuperscript{7} and computed tomography\textsuperscript{34}, and gradation of TR severity according to VC, which has been shown to be more accurate and reproducible compared to jet area or visual assessment\textsuperscript{15,35} and the most prognostic indicator of TR severity\textsuperscript{36}. By integrating TLA with annulus 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-to-closure area, in which closure area reflects both annular area and tenting. Future studies may advance the utility 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.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

We would like to thank the cardiac sonographers at the Hammersmith Hospital and Massachusetts General Hospital for their excellence in acquiring the echocardiographic images that made this study possible.

**Sources of Funding**

Dr. Afilalo holds a Clinical Research Scholars Junior I Career Award from the Fonds de la Recherche en Santé du Québec (FRSQ).

**References**


Figure 1. Tricuspid Leaflet Area, Annulus Area, and Tenting Volume in Three Groups

Compared with healthy controls, PH patients had greater median tricuspid leaflet area (TLA), annulus area, and tenting volume. Although TLA was similar in PH patients with severe TR and non-severe TR, annulus area was significantly larger in those with severe TR such that the ratio of TLA-to-annulus area was insufficient to maintain valvular competency. Sensitivity analysis showed that these results were not unduly influenced by outlier values.
Figure 2. Leaflet Area-to-Closure Area Ratio Is Correlated with Severity of TR
The tricuspid leaflet area (TLA)-to-annulus area ratio was found to be inversely correlated with the severity of TR as measured by vena contracta width (R=-0.66, P<0.0001).
Figure 3. Leaflet Area-to-Closure Area Ratio Discriminates Severe TR (ROC Curve)
Receiver operating characteristic (ROC) analysis showing that the tricuspid leaflet area (TLA)-to-annulus area ratio discriminated between PH patients with vs. without severe TR (odds ratio 68.7, 95% confidence interval 16.2, 292.7), with an area under the ROC curve of 0.9206 and an optimal cutoff value of 1.78.
Figure 4. TR Severity as a Function of Leaflet Area and Closure Area < or > Median
PH patients with large tricuspid leaflet area (TLA) and small closure area had the least TR (far left), while those with small TLA and large closure area had the most TR (far right).
Figure 5. Three-Dimensional Renderings of Open Tricuspid Leaflet Area
Demonstrative renderings of the tricuspid leaflet complex used to calculate tricuspid leaflet area (TAL). To generate these 3-D models, the tricuspid leaflets were manually traced in the open position on successive rotational long-axis planes and then reconstructed using the Omni4D statistical software package.
<table>
<thead>
<tr>
<th>Clinical Characteristics of PH Patients</th>
<th>Severe TR (n=53)</th>
<th>Non-severe 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</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 etiology</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Pre-capillary</td>
<td>33 (62.3)</td>
<td>101 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Post-capillary</td>
<td>20 (37.7)</td>
<td>101 (50.0)</td>
<td></td>
</tr>
<tr>
<td>PH therapy</td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>None</td>
<td>7 (13.2)</td>
<td>22 (10.9)</td>
<td></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>

Abbreviations: Q1, quartile 1; Q3, quartile 3; TR, tricuspid regurgitation; NYHA, New York Heart Association; PH, pulmonary hypertension; PDE5, phosphodiesterase-5. Severe TR defined as average vena contracta width ≥7 mm, non-severe TR defined as <7 mm.
Table 2
Echocardiography Parameters of PH Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe TR (n=53)</th>
<th>Non-severe TR (n=202)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-D 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-D 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, mm Hg</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>&lt;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 (43.5, 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, cm</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, cm</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, cm</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-to-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-to-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>

Abbreviations: TR, tricuspid regurgitation; PISA, proximal isovelocity surface area; ERO, effective regurgitant orifice; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; LV, left ventricle. Severe TR defined as average vena contracta width ≥7 mm, non-severe TR defined as <7 mm.
Table 3
Linear Regression to Predict TR Vena Contracta (Log)

<table>
<thead>
<tr>
<th></th>
<th>Univariable Analysis</th>
<th></th>
<th>Multivariable Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
<td>P-value</td>
<td>Coefficient</td>
</tr>
<tr>
<td>Leaflet area, per cm</td>
<td>−0.010</td>
<td>(−0.025, 0.005)</td>
<td>0.18</td>
<td>−0.036</td>
</tr>
<tr>
<td>Closure area, per cm</td>
<td>0.117</td>
<td>(0.097, 0.137)</td>
<td>&lt;0.001</td>
<td>0.116</td>
</tr>
<tr>
<td>Tenting volume, per cm</td>
<td>0.384</td>
<td>(0.314, 0.453)</td>
<td>&lt;0.001</td>
<td>0.298</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>
</tr>
<tr>
<td>PASP, per mm Hg</td>
<td>0.002</td>
<td>(−0.001, 0.005)</td>
<td>0.30</td>
<td>0.0008</td>
</tr>
<tr>
<td>Age, per year</td>
<td>−0.001</td>
<td>(−0.006, 0.003)</td>
<td>0.57</td>
<td>−0.003</td>
</tr>
<tr>
<td>Female</td>
<td>−0.030</td>
<td>(−0.170, 0.111)</td>
<td>0.68</td>
<td>−0.026</td>
</tr>
<tr>
<td>Pre-capillary etiology</td>
<td>0.315</td>
<td>(0.260, 0.370)</td>
<td>&lt;0.001</td>
<td>0.134</td>
</tr>
</tbody>
</table>

Abbreviations: PASP, pulmonary artery systolic pressure; RV, right ventricle.