Pathogenic structural heart changes in early tricuspid regurgitation

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ABSTRACT

Objective: Severe, late functional tricuspid regurgitation is characterized by annulus dilation, right ventricular enlargement, and papillary muscle displacement with leaflet tethering. However, the early stages of mild tricuspid regurgitation and its progression are poorly understood. This study examined structural heart changes in mild, early tricuspid regurgitation.

Methods: Sequential patients undergoing cardiac computed tomography and transthoracic echocardiography with tricuspid regurgitation were identified and evaluated. The tricuspid annulus area and chamber volumes were measured by computed tomography angiography and categorized by tricuspid regurgitation severity.

Results: Patients (n = 622) were divided into 3 groups by tricuspid regurgitation severity: no/trace (n = 386), mild (n = 178), and moderate/severe tricuspid regurgitation (n = 58). Annulus area was highly dependent on and proportional to regurgitation severity and correlated with both right/left atrial enlargement. Annulus area most strongly correlated with right and left atrial volume, and the annulus shape changed from elliptical to circular in moderate/severe tricuspid regurgitation. Mild tricuspid regurgitation was associated with less right/left atrial enlargement than significant tricuspid regurgitation, normal right ventricular size, and annular dilation. Significant tricuspid regurgitation was associated with annular dilation, circularization, and right ventricular enlargement. Mild and significant tricuspid regurgitation were differentiated by annulus area and indexed right ventricular volume.

Conclusions: Tricuspid annular dilation and right/left atrial enlargement comprise early events in mild functional tricuspid regurgitation. Atrial enlargement occurs before right ventricular dilation, which occurs late, when tricuspid regurgitation is severe. Atrial volume and tricuspid annular dilation are early and sensitive indicators of tricuspid regurgitation significance. (J Thorac Cardiovasc Surg 2015;150:323-30)

Method of TAA measurement. TAA was measured in a plane defined by the tricuspid leaflets' most basal attachments. Measurements of area and major and minor diameters are shown.

Central Message

Early TR causes annular dilation and atrial enlargement, which may be useful in decision making for intervention.

Perspective

Functional TR is associated with late postoperative morbidity and mortality. Its early stages are associated with annular dilation and biatrial enlargement. RV enlargement occurs late, and each of these effects occurs in proportion to TR severity. Understanding longitudinal structural changes in TR may permit early intervention to prevent permanent structural changes.

See Editorial Commentary page 331.

Functional tricuspid regurgitation (TR) is a potent risk factor for all-cause mortality in valvular heart disease.¹ It typically results from left valve disease (LVD) and often fails to improve after successful left valve surgery despite beneficial postoperative hemodynamics. TR is

also associated with increased late postoperative morbidity and mortality.²⁻⁷ The timing of tricuspid valve surgery is important because patients with TR have anemia, organ dysfunction, and right ventricular (RV) dilatation, which also are associated with poor surgical outcomes.⁸

Structural heart changes in severe TR are well described and include tricuspid annular dilation and RV and right atrial (RA) enlargement. Tricuspid annuloplasty has favorable effects on right heart structure,⁹⁻¹¹ and early intervention can prevent right heart dilation and TR progression.¹²

Although structural changes in severe TR are well described, anatomic changes in early, mild TR are not well known. This study examined cardiac structural changes in

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Abbreviations and Acronyms

AF	= atrial fibrillation
CTA	= computed tomography angiography
LA	= left atrial
LV	= left ventricular
LVD	= left valve disease
LVEF	= left ventricular ejection fraction
PH	= pulmonary hypertension
RA	= right atrial
RV	= right ventricular
TAA	= tricuspid annulus area
TR	= tricuspid regurgitation

mild/early TR and compared them with late/severe TR. Recognizing these early structural changes in TR would be useful for therapy and its timing, especially as less-invasive tricuspid repair becomes available.¹³

MATERIALS AND METHODS

A total of 641 sequential patients with both computed tomography angiography (CTA) and transthoracic echocardiography were identified from the Minneapolis Heart Institute Advanced Imaging database. Institutional review board approval was obtained for data collection, analysis, and patient follow-up.

TR was assessed using categorization of Doppler color flow images.¹⁴ Clinical data were collected from the electronic medical record, and patients were classified into 3 groups according to echocardiographic TR severity: none/trace, mild, and moderate/severe (Figure 1).

CTA is a validated, accurate method for measuring right heart volumes^{15,16} and was used to measure chamber volumes and annulus area using Vital Images (Toshiba, Minato, Tokyo) VITREA software. The tricuspid annulus plane was identified from 3-dimensional multiplanar reformat CTA data in diastole. Major and minor diameters, and annulus area were measured (Figure 2). RA, RV, left atrial (LA), and left ventricular (LV) long axes and areas were measured using CTA 4-chamber and orthogonal 2-chamber views (Figure 3). RA, RV, and LA volumes were calculated at mid-diastole using Simpson's method. Chamber volume indices were defined as volume normalized to body surface area. Pulmonary hypertension (PH) was defined as Doppler RV-RA pressure gradient 40 mm Hg or greater, and severe PH was defined as 60 mm Hg or greater. The presence/absence and TR severity were assessed using multiple transthoracic echocardiography windows. Patients were hemodynamically stable at the time of computed tomography and echocardiography imaging.

All patients underwent comprehensive 2-dimensional echocardiography, including Doppler examination of aortic stenosis severity. TV leaflet anatomy and hepatic venous flow patterns were assessed using the parasternal RV inflow, parasternal short-axis, apical 4-chamber, and subcostal views. Mild TR was defined as a small central jet, moderate TR was defined as an intermediate jet, and severe TR was defined as a large jet in the presence of TV leaflet malcoaptation or systolic hepatic vein flow reversal. Pulmonary artery systolic pressure was estimated from the TR jet using the view with maximal velocity, and RA pressure was estimated from inferior vena cava diameter, inspiratory collapse, or direct jugular vein examination. The average TR jet value was assessed during 30 seconds in all atrial fibrillation (AF) cases. Echocardiographic TR was classified into 3 grades: none/trace, mild, or moderate/severe, as noted earlier. The time between CTA and echocardiography was 30 days or less.

Statistical Analysis

Variables were summarized by TR group as median (25th, 75th percentile) for continuous covariates and number and percentage with characteristic for categorical variables. Comparisons between the TR groups were done using the Kruskal–Wallis test for continuous covariates and Pearson's chi-square or Fisher exact tests for categorical variables. The Pearson correlation between cardiac chamber volumes and tricuspid annular area (TAA) was computed.

Univariable and multivariable polytomous (multinomial) logistic regression analysis identified independent and co-predictors of mild TR and moderate/severe TR. We graphically assessed the linearity assumption using restricted cubic splines to flexibly model the relationship between the covariate and the log odds. The linearity assumption was reasonable for all covariates except age and ejection fraction. We found that the relationship could be adequately modeled using a linear spline with knot points at 50 years and 65%, respectively. Covariates in the multivariable model were selected using stepwise variable selection (*P* value for reentry and to stay $\leq .05$). All statistical analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 641 patients with CTA and echocardiography studies were identified. Patients were excluded from the study for the following reasons: prior tricuspid annuloplasty (*n* = 1), implanted LV assist device (*n* = 2), RV tumor (*n* = 1), congenital heart disease (*n* = 2), insufficient or uninterpretable echocardiography data (*n* = 10), and suboptimal computed tomography image quality (*n* = 3). The resulting 622 cases were divided into 3 groups by TR severity: no/trace TR (*n* = 386), mild TR (*n* = 178), and moderate/severe TR (*n* = 58).

Clinical Characteristics

Table 1 shows the clinical characteristics of the 3 patient groups. The median age and percentage of patients with AF and LVD were significantly lower for no/trace TR than the other 2 TR groups. Median body surface area decreased in proportion to increasing TR severity, whereas PH (≥ 40 mm Hg) increased proportionally to increasing TR severity. In moderate/severe TR, left ventricular ejection fraction (LVEF) was lower and PH was more prevalent.

Annulus Comparison

Table 2 compares TAA and shape by TR group. In no/trace and mild TR the annulus maintained an elliptical shape, whereas in moderate/severe TR there was annular circularization (less eccentric) according to the minor/major tricuspid annulus diameter quotient. TAA was larger in moderate TR than in mild TR and proportional to TR severity (*P* < .0001). TAA in moderate/severe TR was larger than in trace and mild TR. TAA thus progressively enlarged and circularized with increasing TR severity.

Atrial and Ventricular Volumes

Table 2 shows RA and LA volumes by TR severity. RA and LA volume and respective volume indices each

355 consecutive cases with 3DCT and echocardiography

FIGURE 1. Patient groups and characteristics. Patient distribution and groups according to echocardiographically defined TR (none/trace, mild, and moderate/severe). TR, Tricuspid regurgitation; 3DCT, 3-dimensional computed tomography.

increased proportionally to TR severity ($P < .0001$). RV volume and index did not differ between no/trace and mild TR, but was significantly dilated in severe TR ($P < .0001$). LV volume index also increased proportionally to increasing TR severity ($P = .0002$).

Correlation Across Tricuspid Regurgitation Severity: Tricuspid Annulus Area, Right Atrial and Left Atrial Volume, and Right Ventricular Volume

Correlations for TAA, RA/RV, and LA volumes by TR severity are shown in Figure 4. Within the mild TR group, the strongest correlate of TAA was RA volume ($r = 0.74$, $P < .0001$) (Figure 4, A). Figure 4, B shows a slightly lower correlation between the TAA and RV volume ($r = 0.57$, $P < .0001$). RA and RV volumes were positively correlated ($r = 0.56$, $P < .0001$) (Figure 4, C). RA and LA volume showed moderately strong correlation ($r = 0.67$, $P < .0001$) (Figure 4, D).

Univariable and Multivariable Analyses

Univariable and multivariable multinomial analyses differentiating no/trace from mild TR are shown in Tables 3 and 4. Variables associated with TR progression from no/trace to mild were increased normalized TAA, increased RA volume index, increased LA volume index, and the presence of LVD, AF, and PH (>40 mm Hg). For age greater than 50 years, age increase was associated with TR progression from no/trace to mild. Multivariable modeling identified increased normalized TAA, increased LA volume index, increased LVEF (for ejection fraction $>65\%$), and the presence of PH (>40 mm Hg) as independent predictors of TR progression from no/trace to mild (Table 4).

Similar univariable and multivariable analyses differentiating mild from moderate/severe TR are shown in Tables 3 and 4. Variables associated with TR progression from mild to moderate/severe were increased normalized TAA, increased RA volume index, increased RV volume index, increased LA volume index, and the presence of LVD and PH (both moderate and severe). Increasing age up to 50 years was associated with a decreased chance of progression from mild to moderate/severe TR. Multivariable modeling identified increased normalized TAA, increased RV volume index, female gender, and the presence of PH (>40 mm Hg) as independent predictors of progression of TR from mild to moderate/severe TR (Table 4). An increased LVEF up to 65% was protective against moving from mild to moderate/severe TR (Table 4).

DISCUSSION

Structural heart changes in severe TR are well known and include tricuspid annular dilation, leaflet tethering, RV dilation, and papillary muscle displacement.¹⁷⁻²⁷ This study sought to understand early cardiac structural changes in TR to delineate its pathologic onset. We characterized and compared structural heart changes in no/trace TR, mild

FIGURE 2. Method of TAA measurement. TAA was measured in a plane defined by the tricuspid leaflets' most basal attachments. Measurements of area, major and minor diameters, are shown.

FIGURE 3. Graphic methods for image assessment. The long axis was measured from the 4-chamber view (A) and orthogonal to this of 4-chamber view (B). RA and RV areas were measured by manual tracing from these views. RA and RV volume were calculated using Simpson's method.

TR, and moderate/severe TR using cardiac CTA for enhanced cardiac structural measurement.^{8,18,27-30}

Tricuspid Regurgitation: Cardiac Structural Changes Across Tricuspid Regurgitation Severity

The pathoanatomic changes among none/trace, mild, and moderate/severe TR suggest that annular dilation and circularization with biatrial enlargement (especially the LA) are important structural alterations across TR progression. The annular area increase and its correlation with RA volume may occur as the atria enlarge, tethering the

annulus in the process. The tricuspid annular correlation with LA volume likely reflects worsening left heart hemodynamics.

These changes may occur through hemodynamics (before LVEF decrease) that produce PH and subsequent right heart failure with RV/RA dilation and annular remodeling.^{17,23,31,32}

Interesting implications arise from these annulus findings concerning flexible versus rigid annuloplasty rings. Specifically, ring design should reflect the 3-dimensional natural ring shape, a feature flexible rings should incorporate to

TABLE 1. Patient characteristics

	No/trace TR (n = 386)	Mild TR (n = 178)	Moderate/severe TR (n = 58)	
	Median (25th, 75th percentile) or N (%)			P value*
Age (y)	62 (53, 70)	68 (57, 74)	72 (58, 82)	<.001
Male gender	216 (56.0)	87 (48.9)	21 (36.2)	.012
Body surface area (m ²)	2.00 (1.82, 2.21)	1.99 (1.77, 2.18)	1.88 (1.73, 2.01)	<.001
Ischemic heart disease	193 (50)	85 (47.8)	27 (46.6)	.817
Hypertension	43 (63.0)	114 (64.0)	38 (65.5)	.916
Diabetes mellitus	77 (19.9)	31 (17.4)	7 (12.1)	.322
Cardiomyopathy	10 (2.6)	8 (4.5)	5 (8.6)	.059
Chronic obstructive pulmonary disease	24 (6.2)	14 (7.9)	8 (13.8)	.113
Chronic renal disease	20 (5.2)	9 (5.1)	10 (17.2)	.005
Chronic heart failure	35 (9.1)	28 (15.7)	15 (25.9)	<.001
AF	57 (14.8)	52 (29.2)	24 (41.4)	<.001
LVD	58 (15)	59 (33.1)	31 (53.4)	<.001
Aortic valve disease	39 (67.2)	32 (54.2)	15 (48.4)	
Mitral valve disease	17 (29.3)	24 (40.7)	12 (38.7)	
Aortic + mitral disease	2 (3.5)	3 (5.1)	4 (12.9)	
Pulmonary HTN >60 mm Hg	2 (0.5)	3 (1.7)	14 (24.1)	<.001
Pulmonary HTN >40 mm Hg	30 (7.8)	68 (38.2)	36 (62.1)	<.001
Ejection fraction (%)	60 (55, 65)	60 (55, 65)	57.5 (45, 65)	.018

AF, Atrial fibrillation; HTN, hypertension; LVD, left valve disease; TR, tricuspid regurgitation. *Comparison of the median covariate value between TR groups using Kruskal-Wallis test for continuous covariates. Comparison of the proportion between TR groups using Pearson's chi-square test or Fisher exact test (when the minimum expected cell count is <5) for categoric covariates.

TABLE 2. Tricuspid annulus and cardiac chambers

	No TR/trace (n = 386)	Mild TR (n = 178)	Moderate/severe TR (n = 58)	P value*
	Median (25th, 75th percentile)			
Major annulus diameter (mm)	45.7 (42.7, 50)	47.6 (43, 52.6)	49.8 (45.9, 53.8)	<.001
Minor annulus diameter (mm)	36 (32.4, 39.1)	36.9 (33.5, 41.2)	42.7 (38.6, 44.6)	<.001
Annulus area, TAA (mm ²)	1305 (1124, 1475)	1422 (1201, 1648)	1622 (1438, 1826)	<.001
Normalized TAA (mm ² /m ²)	650 (560, 740)	713 (624, 824)	888 (810, 952)	<.001
Minor TAD/major TAD	0.8 (0.71, 0.86)	0.81 (0.73, 0.87)	0.86 (0.78, 0.9)	<.001
RA volume (mL)	85 (71, 106)	100 (77, 124)	139 (93, 178)	<.001
RA volume index (mL/m ²)	43 (36, 52)	52 (40, 62)	71 (55, 92)	<.001
RV volume (mL)	118 (94, 147)	117 (96, 152)	140 (101, 188)	.01
RV volume index (mL/m ²)	43 (36, 52)	52 (40, 62)	71 (55, 92)	<.001
LA volume (mL)	87 (72, 108)	102 (79, 132)	113 (84, 149)	<.001
LA volume index (mL/m ²)	44 (36, 53)	51 (41, 65)	59 (45, 76)	<.001
LV volume (mL)	115 (93, 137)	113 (91, 144)	114 (84, 141)	.887
LV volume index (mL/m ²)	56 (47, 65)	57 (48, 70)	64 (50, 75)	.025

LA, Left atrial; LV, left ventricular; RA, right arterial; RV, right ventricular; TAA, tricuspid annulus area; TAD, tricuspid annulus diameter; TR, tricuspid regurgitation. *Comparison of the median covariate value between TR groups using Kruskal–Wallis test for continuous covariates.

prevent not only dilation but also circularization. It is at present unclear whether there are functional implications, but if so, rigid annuloplasty ring structures that maintain the native cross-section with proper proportions might have better late outcome in preventing recurrent TR.

Atrial Dilation, Tricuspid Regurgitation, and Atrial Fibrillation

These data show that AF is a clinical event that may appear early, heralding structural change because it is associated with and differentiates mild TR from no/trace TR.

FIGURE 4. Four panel graphs showing linear correlations among RA/RV volumes and TAA. A, RA volume is highly correlated with TAA. B, RV volume and TAA are correlated, but less well than RA volume. C, RA and RV volume correlation is shown. A significant but relatively low correlation was found. D, LA volume and RA volume are correlated, better than RA and RV volume. LA, Left atrial; RA, right atrial; RV, right ventricular; TAA, tricuspid annulus area; TR, tricuspid regurgitation.

TABLE 3. Univariable multinomial models

	No/trace TR vs mild TR			Mild TR vs moderate/severe TR		
	<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI
n, TAA (per 10 mm increase)	<.001	1.03	1.02-1.05	<.001	1.06	1.04-1.08
RA volume index (per 5 mL/ m ² increase)	<.001	1.17	1.10-1.23	<.001	1.19	1.12-1.27
RV volume index (per 5 mL/ m ² increase)	.198	1.04	0.981-1.09	<.001	1.23	1.13-1.33
LA volume index (per 5 mL/ m ² increase)	<.001	1.19	1.12-1.27	.017	1.10	1.02-1.18
LV volume index (per 5 mL/ m ² increase)	.078	1.05	0.995-1.11	.123	1.07	0.983-1.15
LVD	<.001	2.80	1.84-4.26	.006	2.32	1.27-4.23
AF	<.001	2.38	1.55-3.65	.087	1.71	0.925-3.16
Age (per 10-y increase <50 y)	.541	0.88	0.595-1.31	.029	0.533	0.303-0.937
Age (per 10-y increase >50 y)	<.001	1.33	1.12-1.59	.003	1.52	1.15-2.00
Gender (female)	.117	1.33	0.931-1.90	.094	1.68	0.914-3.10
PH (>60 mm Hg)	.194	3.29	0.545-19.87	<.001	18.56	5.11-67.4
PH (>40 mm Hg)	<.001	7.34	4.54-11.85	.002	2.65	1.44-4.87
LVEF (per 5% increase up to 65%)	.020	0.897	0.818-0.983	.016	0.861	0.762-0.972
LVEF (per 5% increase >65%)	.002	1.84	1.24-2.71	.871	1.05	0.580-1.90

AF, Atrial fibrillation; CI, confidence interval; LA, left atrial; LV, left ventricular; LVD, left valve disease; LVEF, left ventricular ejection fraction; OR, odds ratio; PH, pulmonary hypertension; RA, right atrial; RV, right ventricular; TAA, tricuspid annulus area; TR, tricuspid regurgitation.

However, the multivariable modeling found that enlargement of the annulus and left atrium in the setting of PH greater than 40 mm Hg correlates with TR severity better than AF. These data do not imply cause-and-effect between AF and structural changes (eg, AF causing enlarged atria) because the inverse could also be true, namely, enlarged atria may cause TR and AF.

Clinical Implications

This study may help understand the timing for optimal TR treatment. Annular enlargement and circularization along with RA/LA enlargement herald the structurally normal heart becoming affected by TR. Further effects

continue the pathologic cascade, progressing through annular circularization and dilation, biatrial enlargement, and eventual RV dilation. It is unclear when these pathologic changes become irreversible with heart failure and AF.

Chronic AF is a risk factor for progressive TR.^{33,34} AF in the setting of TR may reflect and at the same time facilitate further negative structural remodeling as a component of severe end-stage TR. AF may cause parallel annular and RA enlargement, which in turn facilitate more AF. This speculation is supported by clinical observations of the Maze that can prevent TR progression after mitral valve surgery.^{35,36}

TABLE 4. Multivariable multinomial models

	No/trace TR vs mild TR			Mild TR vs moderate/severe TR		
	<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI
n, TAA (per 10-mm increase)	<.001	1.03	1.01-1.04	<.001	1.06	1.03-1.09
RV volume index (per 5 mL/ m ² increase)	.839	0.992	0.924-1.07	<.001	1.21	1.09-1.35
LA volume index (per 5 mL/ m ² increase)	.002	1.11	1.04-1.19	.180	0.936	0.850-1.03
Gender (female)	.201	1.15	0.924-1.45	<.001	2.12	1.41-3.19
PH (>40 mm Hg)	<.001	6.00	3.63-9.93	.016	2.42	1.17-5.00
LVEF (per 5% increase up to 65%)	.344	0.951	0.858-1.05	.022	0.838	0.720-0.975
LVEF (per 5% increase >65%)	.018	1.66	1.09-2.53	.976	0.989	0.466-2.10

CI, Confidence interval; LA, left atrial; LVEF, left ventricular ejection fraction; OR, odds ratio; PH, pulmonary hypertension; RV, right ventricular; TAA, tricuspid annulus area; TR, tricuspid regurgitation.

This study suggests that TR repair is wise and provides evidence that early repair may be an optimal TR treatment time. Annular dilation in mild TR is likely irreversible because it likely involved collagen and matrix synthesis. The tricuspid annulus frequently remains dilated even after successful left heart surgery.^{37,38} Also supporting this concept is that prophylactic tricuspid annuloplasty performs well in the long term because it specifically targets tricuspid annular dilation.^{19,39}

Severe TR is accompanied by RV expansion, and this dilation is often irreversible, as are annular changes.^{38,40} RV function is an independent factor for mortality among patients with TR,⁴¹ and TR treatment often does not improve mortality among patients with RV dysfunction. Each of these observations together suggest that early TR treatment is optimal and could improve and preserve RV function.^{42,43}

Study Limitations

This study was retrospective, and selection bias may have occurred because all subjects underwent computed tomography and 2-dimensional echocardiography for clinical reasons. It is known that RA/RV/inferior vena cava enlargement can occur in other conditions and can be normal in acute, severe TR.⁴⁴

TR assessment was by color flow Doppler and hepatic vein flow reversal, which can be less reliable in assessing TR grade in severe disease. The study established associations, but cause and effect cannot be implicated for altered anatomy.

CONCLUSIONS

Early structural heart changes in functional TR include annular dilation in conjunction with RA/LA enlargement. These occur in proportion to TR severity. RV dilation is a late event seen in moderate-severe TR. Understanding the longitudinal structural changes of TR may assist in identifying and intervening early to prevent deleterious permanent deleterious pathology.

Conflict of Interest Statement

Erin Spinner reports equity ownership in Edwards Lifesciences Robert Schwartz reports consulting fees from Boston Scientific and Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

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