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ORIGINAL ARTICLE

Atrial Functional Tricuspid Regurgitation: Novel Definition and Impact on Prognosis

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BACKGROUND: Atrial functional tricuspid regurgitation (atrial TR) has received growing recognition as a TR entity with a distinct cause owing to its independence from valvular tethering as the predominant mechanism underlying TR. However, characterization of atrial TR varies, and a universal definition is lacking.

METHODS: In total, 651 patients with significant functional TR were analyzed, including 438 conservatively treated individuals and 213 patients who received transcatheter tricuspid valve repair (TTVR). Based on a clustering approach, we defined atrial TR as tricuspid valve (TV) tenting height ≤10 mm, midventricular right ventricular diameter ≤38 mm, and left ventricular ejection fraction ≥50%.

RESULTS: Patients with atrial TR were more often females, had higher right ventricular fractional area change, higher left ventricular ejection fraction, and lower LV end-diastolic diameter, TV tenting area and height, lower right ventricular and tricuspid annular size, enlarged, but lower right atrial area and lower TV effective regurgitant orifice area (all $P<0.05$). Patients with atrial TR had significantly better long-term survival than non-atrial TR in the conservatively treated TR cohort ($P<0.01$, n=438). Atrial TR was independently associated with a lower rate of the combined end point of mortality and heart failure hospitalization at 1-year follow-up in the TTVR cohort (hazard ratio, 0.39; $P<0.05$, n=213). TR degree was significantly reduced after TTVR in non-atrial and atrial TR ($P<0.01$). Functional parameters significantly improved following TTVR independent of TR cause ($P<0.05$).

CONCLUSIONS: An echocardiography-based atrial TR definition is associated with prognostic relevance in patients with functional TR in conservatively treated TR and after TTVR.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: echocardiography ■ heart failure ■ hospitalization ■ survival ■ tricuspid valve

Tricuspid regurgitation (TR) is associated with heart failure and reduced survival.[1–3] Within a short-time period, transcatheter tricuspid valve repair (TTVR) for TR has evolved from innovation to clinical reality. Improved survival has been reported in propensity-matched contemporary cohorts undergoing TTVR,[4–6] and dedicated leaflet devices recently received CE mark approval. However, as seen in transcatheter mitral valve (MV) therapies, optimized patient selection remains crucial to improve mortality and morbidity for a highly vulnerable patient group.

Defining TR causes is central for optimized patient selection. However, TR etiologies are more complex than those of mitral regurgitation (MR). As investigations on the MV have gained momentum, atrial MR has increasingly been appreciated as a separate entity with therapeutic and prognostic implications.[7,8] Significant regurgitation of the tricuspid valve (TV) followed suit in this regard and interventional TR treatment as part of clinical trials as well as part of clinical guideline-directed therapy for high-risk patients is becoming clinical reality.[9,10] In the wake of these developments, scientific and

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WHAT IS KNOWN

- Atrial functional tricuspid regurgitation (atrial TR) is characterized by a specific cause and pathophysiology.

WHAT THE STUDY ADDS

- The present analysis identified patients with atrial TR based on 3 echocardiographic parameters and suggests better clinical outcome in patients with atrial TR compared with non-atrial TR in conservative TR treatment and after transcatheter tricuspid valve repair.
- Patient selection for transcatheter tricuspid valve repair remains challenging. The identification of novel TR causes with implications for clinical outcome, such as atrial TR, may provide additional guidance and should be considered in clinical trials.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation/flutter
eGFR	estimated glomerular filtration rate
EROA	effective regurgitant orifice area
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
MV	mitral valve
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RA	right atrial
RCT	randomized controlled trial
RV	right ventricular
sPAP	systolic pulmonary artery pressure
TA	tricuspid annular
TR	tricuspid regurgitation
TTVR	transcatheter tricuspid valve repair
TV	tricuspid valve

clinical interest arose to identify factors that indicate elevated risk in clinical end points in the natural history of TR and after TTVR as well as parameters that associate with adverse procedural and clinical outcomes after TTVR. In that respect, atrial TR still is a neglected entity that may necessitate treatment strategies different from non-atrial TR as the prevailing TR mechanism. Atrial TR is increasingly being recognized as a separate TR entity.[11–14] First described in 2002,[15] definitions of atrial TR vary, however, most commonly a stepwise exclusion of clinical or echocardiographic parameters is used to identify atrial/isolated TR.[1,16–22] Atrial TR, isolated TR and TR in heart failure with preserved ejection fraction appear to reflect similar entities despite minor variations.[1,6,16,17,22] A common feature, however, appears to be the absence of either ventricular (systolic) dysfunction or leaflet tethering.[14] The prognostic significance of atrial TR has not been described thus far. We here report an echocardiography definition of atrial TR with prognostic implications for the natural disease course and after TTVR.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population—TTVR Cohort

The analysis was performed in 304 consecutive patients undergoing edge-to-edge TTVR and PASCAL for symptomatic functional TR at 2 tertiary care centers (Heart Center Leipzig, University of Leipzig, Germany, and University Hospital of the Ludwig-Maximilians Universität, Munich, Germany) from 2016 to 2020. Of these, 138 patients from Leipzig served as the derivation cohort for the atrial TR definition. Clinical and echocardiographic baseline and follow-up data were prospectively collected. Clinical follow-up was done by clinical visits and phone consultation at 30 days and 1 year after TTVR. The inclusion of patients in this study was approved in each center by a local ethics committee or per local practice for clinical data collection. All patients were symptomatic with signs of heart failure. TR therapy was indicated in accordance with international guidelines[9] and heart team consensus rendered all patients at high or prohibitive surgical risk. TTVR was conducted on an off-label or compassionate use basis. Severe aortic valve stenosis, any degree of tricuspid or MV stenosis, a tricuspid or MV anatomy considered unsuitable for edge-to-edge repair and inferior echocardiographic visualization of the TV on transesophageal echocardiography served as exclusion criteria. Unsuitable valve anatomy included conditions that would render grasping of the leaflets unlikely: restricted leaflet mobility due to pacemaker or implantable cardioverter defibrillator leads, an effective regurgitant orifice area (EROA) of >1.5 cm^2, and a TV coaptation gap exceeding 15 mm. Of note, severely impaired right ventricular (RV) function and pulmonary hypertension were not considered exclusion criteria.

Study Population—Conservatively Treated TR Cohort

Patients with significant functional TR were identified from the departmental echocardiographic database at the Leiden University Medical Center (Leiden, the Netherlands) between June 1995 and September 2016. TR severity was classified according to current guidelines by an integrative approach based on qualitative, semiquantitative, and quantitative color Doppler flow data, continuous-wave Doppler data of the regurgitant jet, and assessment of RV and right atrial (RA) dimensions.[23] Patients with primary TR (valve prolapse, active endocarditis, acute rheumatic disease, or tumor) and congenital heart disease were excluded. In addition, patients with incomplete echocardiographic data to assess RV remodeling were excluded. Patients were evaluated with transthoracic echocardiography to assess RV size (measured by tricuspid annular [TA] diameter) and RV systolic function (measured by TA plane systolic excursion). Demographics and clinical data were

collected in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center) and analyzed retrospectively. The analysis was approved by the institutional review board of the Leiden University Medical Center, and the need for patient written informed consent was waived.

General Inclusion and Exclusion Criteria

Patients with severe aortic stenosis or any degree of mitral or tricuspid valve stenosis and MR >grade 2 were excluded in our analysis.

Patients were included in the initial screening steps to establish the atrial TR definition irrespective of the EROA. However, for the data analysis patients with EROA <0.4 cm^2 were excluded to focus specifically on ≥grade 3 TR in both the conservative and TTVR cohorts.

Device and Procedure

The TTVR procedures were performed using the MitraClip (Abbott Cardiovascular, United States) and PASCAL (Edwards Lifesciences, United States) devices.

Study End Points and Follow-Up Assessment

The study end point was defined as the 10-year survival rate in the conservative TR cohort. The combined end point of 1-year mortality and heart failure hospitalization served as the end point in the TTVR cohort. One-year mortality, postprocedural TR grade, New York Heart Association functional class, and 6-minute walk distance served as additional end points in the TTVR cohort. Follow-up clinical and echocardiographic examinations were conducted at 1 month and 1 year after TTVR.

Statistical Analysis

Continuous variables are presented as means and SDs (if normally distributed) or medians with interquartile range when skewed. The normality assumption was evaluated using the Kolmogorov-Smirnov test.

Categorical variables are summarized as number of participants and proportions. Two-group statistical comparisons were conducted using the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables. For repeated measurements of continuous variables, the Wilcoxon signed-rank test was used instead. Mortality rates and rates of heart failure hospitalization were analyzed with Kaplan-Meier estimates and the log-rank test was applied for group comparisons.

Echocardiograms of patients from the derivation cohort were reviewed by 2 investigators and the prevailing TR cause was identified. Heatmaps with hierarchical clustering and principal component analyses based on echocardiographic parameters and atrial fibrillation/flutter (AF) were

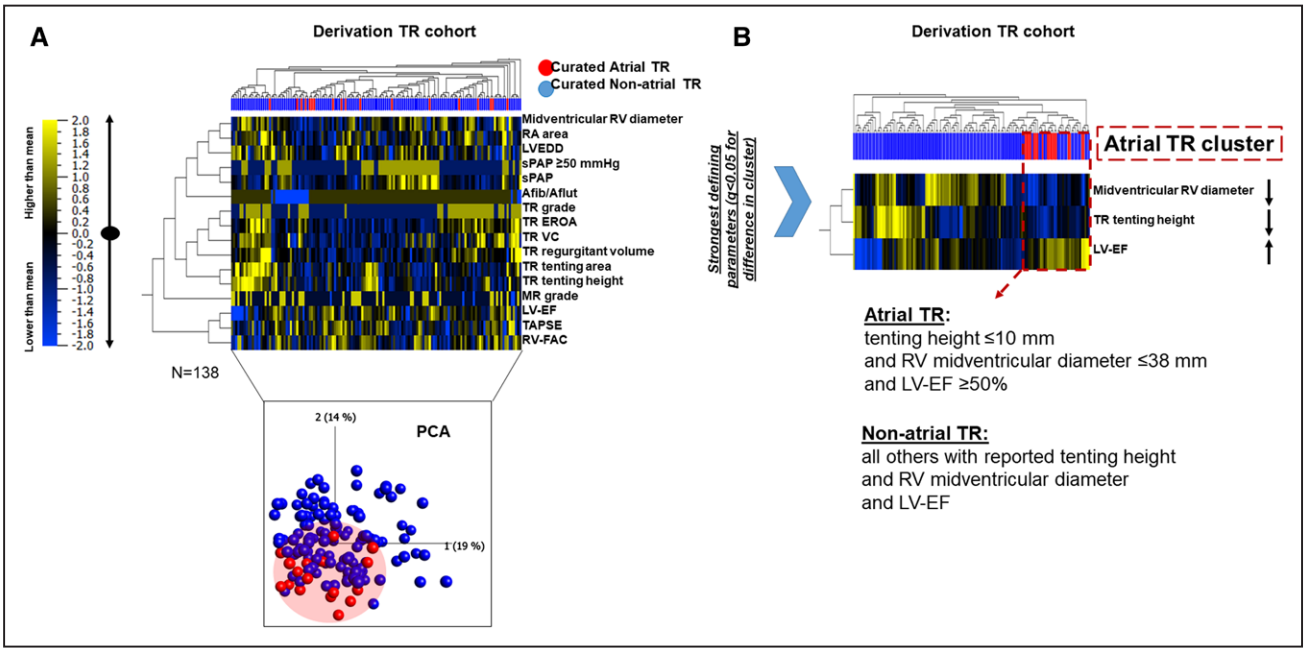

Figure 1. Data analysis pipeline to identify echocardiographic variables that best identify patients with investigator-identified atrial tricuspid regurgitation (TR).

A, Heatmap of all parameters used in the analysis in the exploratory TR cohort (Leipzig transcatheter tricuspid valve repair [TTVR] cohort). Yellow color delineates higher than average values and blue lower than average values for a given parameter (x-orientation). Y-orientation for individual patients with TR. Color coding (blue/red) on top represents patients with TR grouped into atrial or non-atrial TR based on visual inspection of echocardiograms for prevailing TR mechanism by investigators. **Lower**: Principal component analysis (PCA) of all patients with TR in the exploratory cohort including all parameters. Investigator-identified atrial TR cases appear to form a separate cluster in the lower left quadrant suggesting that differences in the input parameters may identify an atrial TR cluster. **B**, Heatmap of 3 echocardiographic parameters identified as echocardiographic parameters that best identify an atrial TR cluster that is enriched in TR cases with investigator-identified atrial TR (false discovery rate: q<0.05 for differences in cluster). Cutoff values for these echocardiographic parameters to define atrial TR were manually curated from the parameter distributions and histograms. LVEDD indicates left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RA, right atrial; RV, right ventricular; RV-FAC, RV-fractional area change; sPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.

performed. The parameters (midventricular RV diameter, RA area, left ventricular (LV) end-diastolic diameter, systolic pulmonary artery pressure (sPAP) ≥50 mm Hg, sPAP (continuous variable), presence of AF, TR grade, TR EROA, vena contracta, TR regurgitant volume, TV tenting area, tenting height, MR grade, LV ejection fraction (LVEF), TA plane systolic excursion, RV-fractional area change) were filtered for the largest impact on cluster enrichment of patients in the atrial TR cluster using *q* value (multiple testing adjusted false discovery rate) cutoffs ($q<0.10$). This strategy was used to weigh cluster enrichment in the atrial cluster and the number of identified parameters that best predict this cluster enrichment.

Cox regression analyses were performed to identify predictors for the occurrence of 1-year mortality or heart failure hospitalization in patients after TTVR. The proportionality of hazards assumption was confirmed for all Cox models. The model was adjusted for all baseline covariates that were significantly different between atrial TR and non-atrial TR in the TTVR cohort in addition to sPAP and AF, which were included for their potential influence on outcome in the light of their etiological role for atrial TR and non-atrial TR.

Statistical analyses were performed with SPSS version 25 (IBM Corporation, United States), Qlucore Omics Explorer 3.7 (Qlucore, Sweden), and GraphPad Prism 8 (GraphPad Software Inc, United States).

RESULTS

Identification of Atrial Functional TR Morphology

In the 138 patients of the derivation cohort, transthoracic and transesophageal echocardiograms were manually reviewed for the prevailing TR mechanism to identify atrial TR. Figure 1A shows a heatmap of echocardiographic and clinical parameter distribution with hierarchical clustering applied to both the parameters and the TR cases. The top label identifies the group assignment of atrial and non-atrial cause. Principal component analysis suggested enrichment of cases with presumed atrial mechanism in a cluster (Figure 1A, bottom). The baseline parameters were next filtered to detect subsets of parameters that best differentiated between atrial and non-atrial clusters ($q<0.05$). This strategy resulted in an enrichment of atrial TR cases in an atrial TR cluster (top label) based on 3 parameters: TV tenting height, midventricular RV diameter, and LVEF. We defined atrial TR based on the following parameters by manual data curation: tenting height ≤10 mm, RV midventricular diameter ≤38 mm, and LVEF: ≥50%. Representative echocardiographic studies of patients with atrial and non-atrial

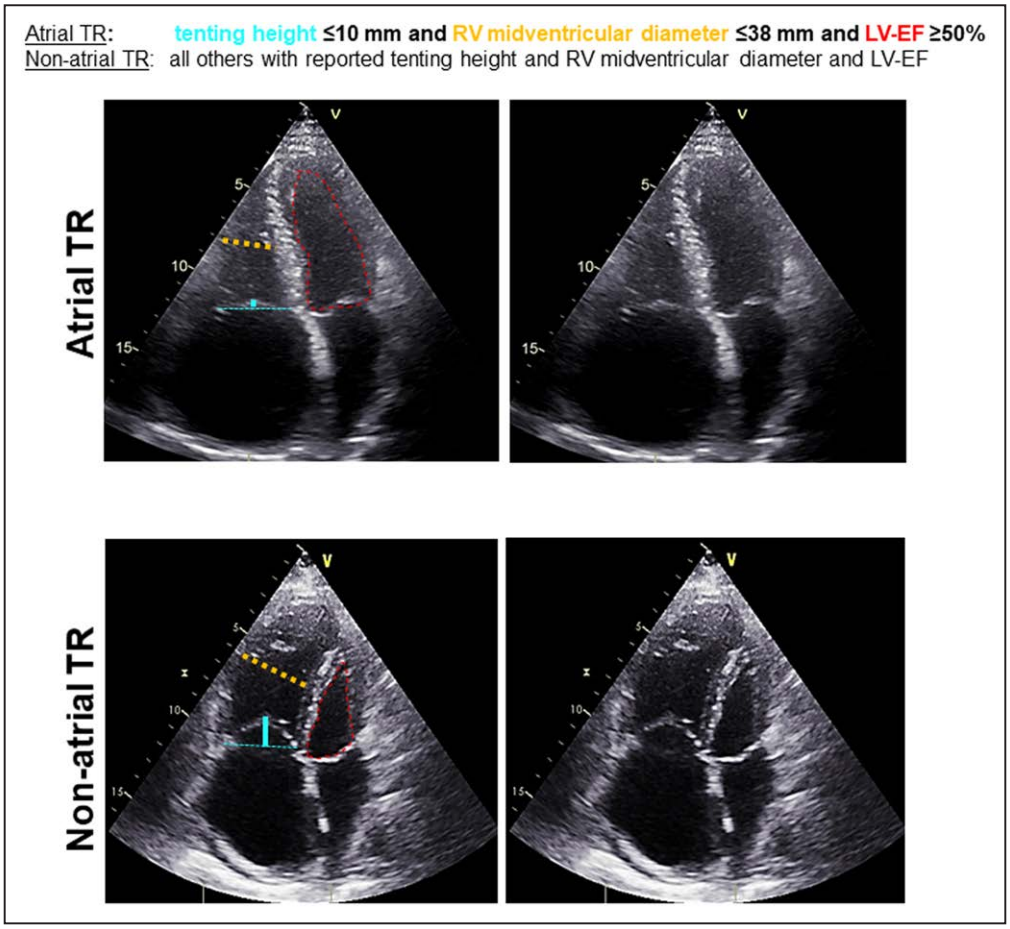

Figure 2. Atrial tricuspid regurgitation (atrial TR) definition.
Representative transthoracic echocardiographic 4 chamber views of patients identified to have non-atrial or atrial TR. LV-EF indicates left ventricular ejection fraction; and RV, right ventricle.

Table. Baseline Clinical and Echocardiographic Characteristics of the Conservatively Treated and TTVR Cohorts

	Conservative			TTVR			
	Non-atrial TR	Atrial TR	*P* value (nonatrial vs atrial)	Non-atrial TR	Atrial TR	*P* value (nonatrial vs atrial)	*P* value (conservative vs TTVR)
N (%)	393 (90)	45 (10)		172 (81)	41 (19)		
Age, y	70 [62; 78]	72 [62; 78]	0.781	78 [75; 82]	79 [76; 83]	0.361	<0.001
Female	178 (45)	28 (62)	0.001	70 (41)	28 (68)	0.001	0.385
BMI	25.7 [23.3; 28.9]	25.6 [24.0; 28.3]	0.737	25.9 [23.1; 29.1]	23.2 [21.8; 27.7]	0.009	0.991
NYHA class III or IV	161 (45)	11 (28)	0.038	156 (93)	33 (83)	0.041	<0.001
AF	213 (57)	26 (61)	0.687	148 (86)	34 (83)	0.611	<0.001
Chronic obstructive pulmonary disease	51 (14)	4 (9)	0.364	40 (23)	2 (5)	0.008	0.034
eGFR, mL/min per 1.73 m^2	63 [45; 82]	70 [60; 86]	0.076	45 [30; 59]	50 [37; 66]	0.288	<0.001
NT-proBNP, pg/ml	-	-	-	2409 [1315; 5637]	1777 [917; 2851]	0.051	-
EuroSCORE II, %	-	-	-	4.6 (2.6; 7.5)	4.6 (3.1; 7.2)	0.844	-
Echocardiography							
TAPSE, mm	14 [11; 17]	16 [14; 19]	0.003	16 [13; 20]	18 [15; 21]	0.074	<0.001
RV-FAC, %	34 [25; 43]	44 [31; 50]	<0.001	39 [33; 46]	41 [35; 53]	0.021	<0.001
LVEF, %	41 [31; 52]	60 [54; 67]	<0.001	55 [46; 60]	61 (57; 66]	<0.001	<0.001
LVEDD, mm	49 [42; 57]	43 [38; 47]	<0.001	49 [44; 54]	46 [40; 51]	0.004	0.019
TR grade			<0.001			0.038	<0.001
5	-	-		15 (9)	-		
4	116 (30)	2 (4)		55 (32)	9 (22)		
3	277 (70)	43 (96)		102 (59)	32 (78)		
MR grade			0.047			0.477	<0.001
0	45 (12)	8 (18)		13 (8)	1 (2)		
1	168 (43)	25 (56)		112 65)	29 (71)		
2	179 (45)	12 (26)		47 (27)	11 (27)		
Tenting height, mm	13 [11; 16]	7 [5; 9]	<0.001	9 [7; 11]	6 [5; 7]	<0.001	<0.001
Tenting area, cm^2	3.8 [2.7; 5.2]	1.5 [0.9; 2.1]	<0.001	1.8 [1.2; 2.6]	1.0 [0.7; 1.8]	<0.001	<0.001
RV size							
Midventricular RV diameter (RV), mm	36 [30; 43]	30 [26; 35]	<0.001	45 [42; 51]	35 [32; 37]	<0.001	<0.001
Tricuspid annular diameter (TA), mm	43 [39; 49]	39 [34; 43]	<0.001	50 [45; 56]	44 (38; 48]	<0.001	<0.001
TA/RV diameter ratio	1.2 [1.1; 1.4]	1.3 [1.1; 1.5]	0.015	1.0 [0.9; 1.2]	1.2 [1.1; 1.3]	0.002	<0.001
RA area, mm^2	29 [22; 35]	25 [19; 32]	0.014	39 [32; 47]	32 [28; 40]	0.003	<0.001
RV length, mm	-	-	-	73 [66; 81]	68 [61; 73]	<0.001	-
sPAP, mm Hg	41 [32; 53]	37 [29; 49]	0.094	40 [32; 51]	40 [34; 47]	0.950	0.671
sPAP ≥50 mm Hg				46 (27)	9 (22)	0.516	0.620
TV EROA, cm^2	0.86 [0.61; 1.28]	0.54 [0.46; 0.72]	<0.001	0.62 [0.50; 0.80)	0.56 [0.43; 0.70]	0.030	<0.001

Data are n (%), or medians (interquartile range). AF indicates atrial fibrillation/flutter; BMI, body mass index; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RA, right atrial; RV, right ventricular; RV-FAC, right ventricular fractional area change; sPAP, estimated systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; and TTVR, transcatheter tricuspid valve repair.

TR mechanism are shown in Figure 2. We validated this identification approach by applying this atrial TR definition to patients from the conservatively treated TR cohort and were able to confirm that the same 3 parameters used for the atrial TR definition led to an enrichment of atrial TR cases in the atrial TR cluster (dashed red line, Figure S1).

Clinical and Echocardiographic Characteristics of Atrial and Non-Atrial Functional TR

Baseline clinical and echocardiographic parameters for the study cohorts stratified by conservative and interventional therapy are shown in the Table. Approximately 15% of patients were classified to have atrial

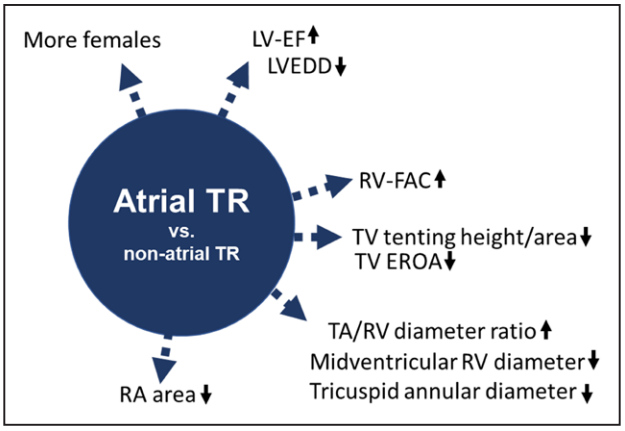

Figure 3. Differences in baseline parameters between non-atrial and atrial tricuspid regurgitation (TR).
BNP indicates B-type natriuretic peptide; EROA, effective regurgitant orifice area; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular; RV-FAC, right ventricular fractional area change; TA, tricuspid annular; TAPSE, TA plane systolic excursion; and TV, tricuspid valve.

TR (Table). Patients with atrial TR were more often female, had higher RV-fractional area change, LVEF, TA/RV diameter ratio (RV geometry/sphericity) and lower TV tenting height, TV tenting area, RA area, RV midventricular and TA annular diameter, TR EROA, and LV end-diastolic diameter, than patients with non-atrial TR (Table and Figure 3). NT-proBNP (N-terminal pro-B-type natriuretic peptide) was not significantly different between atrial TR and non-atrial TR. Notably, while included in most atrial TR definitions, AF had no predictive value for the atrial TR classification. The rate of AF was significantly higher in the TR cohort that underwent TTVR than in patients treated conservatively (Table).

Outcomes of Atrial and Non-atrial Functional TR

TR degree was significantly reduced after TTVR in non-atrial and atrial TR ($P<0.001$; Figure 4A). The majority of patients had TR reduction to at least moderate TR (TR grade ≤grade 2: atrial TR: 86%, non-atrial TR: 81%; $P<0.001$, Figure 4A). New York Heart Association functional class improved in patients with non-atrial and atrial TR after TTVR ($P<0.001$, Figure 4B). The 6-minute walk distance was significantly higher at 1 month of follow-up than at baseline in patients with non-atrial and atrial TR (atrial TR: baseline: 266 m, 1 month: 354 m; $P<0.001$; non-atrial TR: baseline: 224 m, 1 month: 291 m; $P<0.05$, Figure S2). Procedural details and outcomes are summarized in Table S1.

Atrial TR was associated with significantly better survival on long-term follow-up in the conservatively treated TR cohort compared with non-atrial TR (33% versus 57%; $P<0.001$, Figure 5A). In the TTVR cohort, atrial TR compared with non-atrial TR, was associated with a lower rate of the combined end point of mortality and heart failure hospitalization at 1-year follow-up (12% versus 36%; $P=0.017$, Figure 5B). The association of atrial TR with 1-year mortality or heart failure hospitalization remained independent of the influence of New York Heart Association class, RV-fractional area change, LV end-diastolic diameter, EROA, female sex, body mass index, AF, chronic pulmonary disease, TV tenting area, TR grade, TA/RV ratio, RA area, RV length, and sPAP (hazard ratio, 0.39 [95% CI, 0.16–0.98]; $P<0.05$; Table S2).

DISCUSSION

The present study used a bioinformatic strategy to derive an echocardiographic definition of atrial TR. Main findings include: (1) TV tenting height, midventricular RV diameter and LVEF can be used to identify ≈15% of all patients with significant TR with a likely underlying atrial mechanism; (2) patients with atrial TR differed in baseline echocardiographic and clinical parameters from patients with non-atrial TR and had lower tenting heights, tenting areas, RV and TA diameters, higher LVEF and RV-fractional area change, and were more often female; (3) classification as atrial TR was associated with better long-term survival in conservative TR treatment and was independently associated with a lower rate of the combined end point of mortality and heart failure hospitalization following TTVR; and (4) procedural functional results including postprocedural TR grade, New York Heart Association class, and 6-minute walk distance did not differ between atrial and non-atrial TR.

Current guidelines do not emphasize the need to differentiate atrial functional TR from non-atrial functional TR.[9,24] However, growing recognition of atrial TR as a distinct TR mechanism spurred enthusiasm to better define atrial TR and to explore prognostic implications. Consistent with data for the MV,[25] in our analysis, atrial TR had a significantly better prognosis than non-atrial TR. This is the first analysis to report clinical implications of atrial TR following TTVR. The identification of differences in clinical events between atrial and non-atrial TR in both the conservatively treated and TTVR cohorts suggest better long-term survival in atrial TR in the conservatively treated cohort and a lower rate of mortality and HF hospitalization in the TTVR cohort. Only few predictors of adverse outcome in TR[26] and after TTVR[5,27,28] have been identified before. The strongest predictor of adverse outcome in TTVR appears to be procedural failure.[27] In the current analysis, atrial TR was identified as a TR entity of relevance for clinical outcome.

The early classification of TR into pulmonary hypertension related and idiopathic TR[29] was the first attempt to distinguish patients with identifiable primary causes of

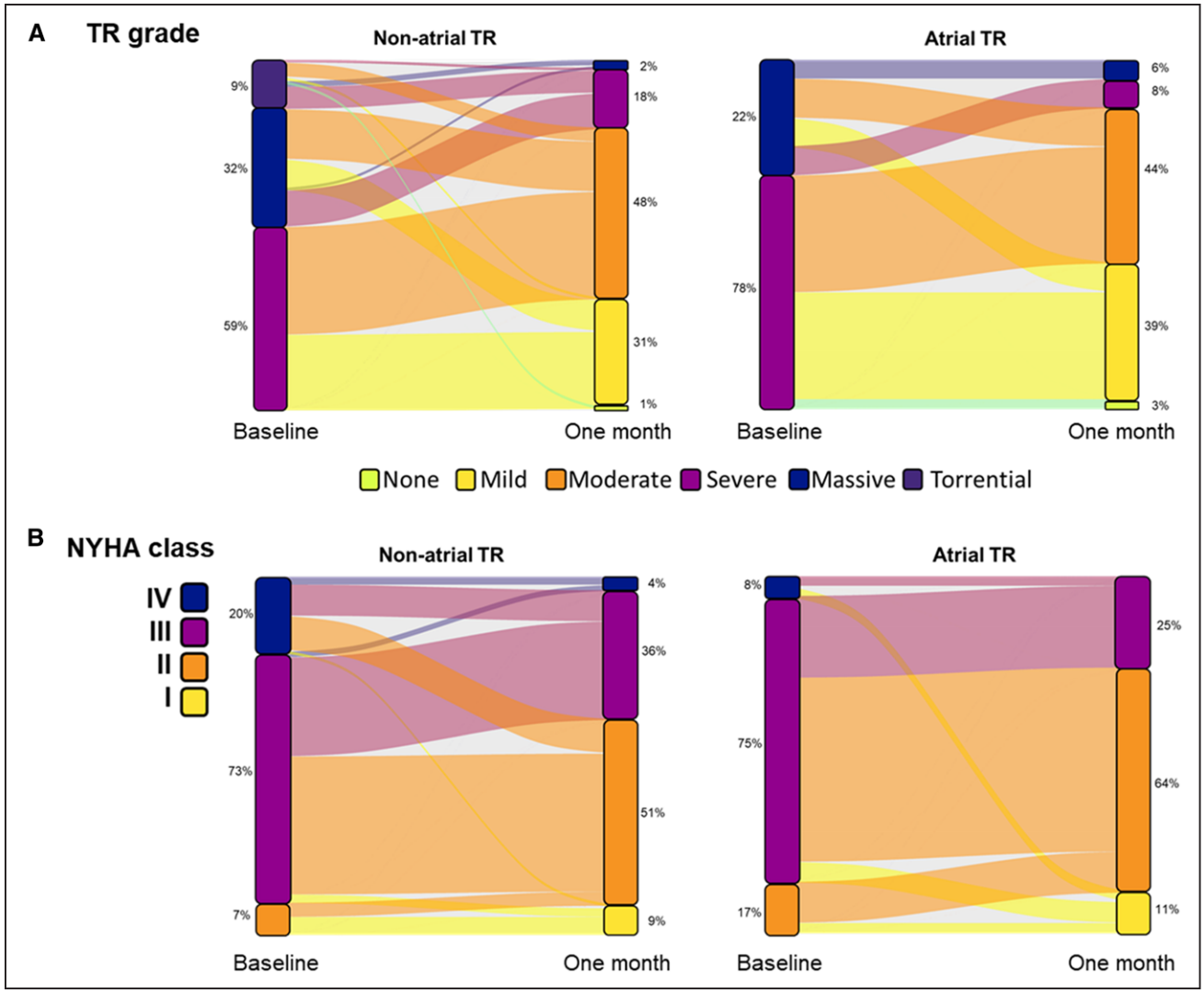

Figure 4. Dynamics in tricuspid regurgitation (TR) grade and New York Heart Association (NYHA) class between baseline and 1-mo follow-up in non-atrial and atrial TR after transcatheter tricuspid valve repair.
A, TR grade and (**B**), NYHA class.

TR (ie, left sided valvular disease, LV systolic dysfunction, and precapillary pulmonary hypertension) from patients without these cardiovascular diseases. More recently, we have come to recognize that the latter patients also represent a unique set of clinical associations, including AF, age, and heart failure with preserved ejection fraction, which can be encompassed by the classification of atrial TR. We, herein, propose a uniform definition of atrial TR, derived from a clustering approach that identified 3 echocardiographic parameters that define atrial TR. It has been noted that atrial TR may be recognized by echocardiography.[30] Our atrial TR definition is solely centered on echocardiographic parameters, thereby basing the definition on parameters that can readily be assessed through standard echocardiographic exams. The proposed atrial TR definition is the first to include morphometric RV parameters and parameters that account for TV tethering.

Important similarities and differences to alternative atrial TR definitions have to be noted: the proposed atrial TR definition excluded patients with LV dysfunction, in line with prior reports.[1,17,21] Also, RV dysfunction that associates with RV dilatation, was previously noted to oppose classification as atrial TR.[31] The proposed TR classification is in line with prior classification schemes in that leaflet tethering is included as a differentiating parameter.[14,32,33]

While sPAP was used to identify isolated/atrial TR before,[1,17] sPAP was not significantly different between atrial and non-atrial TR in our analysis. This finding may be considered a limitation of our definition, however, the longer standing presence of pulmonary hypertension frequently is reflected by altered RV geometry with RV dilatation, a parameter that was part of our atrial TR definition. In addition, in a prior analysis on atrial TR, in patients with AF, those with significant atrial TR had higher sPAP compared with those without significant

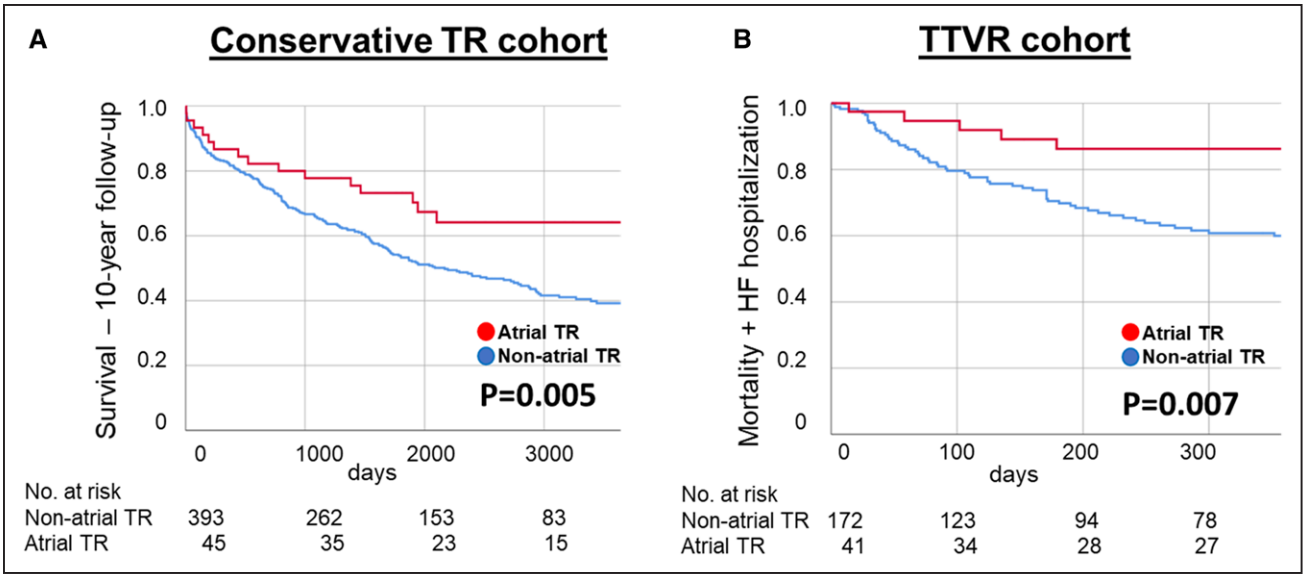

Figure 5. Outcome parameters stratified by tricuspid regurgitation (TR) cause.
A, Survival analysis between non-atrial and atrial TR groups in the conservatively treated cohort over long-term follow-up. **B**, Combined end point of heart failure (HF) hospitalization and mortality between non-atrial and atrial TR groups in the transcatheter tricuspid repair (TTVR) cohort over 1-y follow-up.

TR,[22] suggesting that elevated sPAP may not preclude classification as atrial TR. However, in this analysis, also patients with nonprimary MR of greater or equal to grade 2 were able to get classified as atrial TR, which may be considered a limitation of that atrial TR definition.[22] Patients with MR >grade 2 were excluded in our analysis, as these patients would have likely received combined transcatheter mitral and tricuspid valve repair in the interventional cohort.

The association of atrial TR with AF is conflictingly discussed.[19,29,30] There was no difference between the rate of AF between atrial TR and non-atrial TR in our analysis. Of note, the rate of AF in the TTVR cohort exceeded 80% and may thus not enable differentiation between groups. Moreover, history of AF may not represent the absolute rate of AF as the detection rate of AF likely is suboptimal.[34] Furthermore, the addition of AF to the statistical model did not aid in the selection of investigator-identified criteria to contribute to a definition that resembles these criteria. Rates of AF compare favorably to those reported for isolated TR.[1,19]

Interestingly, RA area was larger in non-atrial TR relative to atrial TR. Larger RA volumes associate with TR in patients with AF.[22] However, RA enlargement[35] was evident in the study cohorts in the present analysis and larger RA areas were noted in patients undergoing TTVR relative to conservative treatment.

Here we report a definition based on morphometric and functional echocardiographic parameters. In our stepwise approach, LV function (LVEF), RV diameter representing RV dilatation, and TV leaflet tethering indicated by tenting height were used to define atrial TR. Of note, RV diameter correlated strongly with TA diameter, suggesting that TA diameter may also have been used in the atrial TR definition.

The proposed atrial TR definition may only be an approximation and imperfections may remain. However, it fills an important gap in that it provides a reproducible means of categorization of this important entity.

Limitations

Our approach to identify atrial TR has limitations. As atrial TR associates with chronic volume overload, ventricular remodeling must be anticipated, and in late-stage atrial TR, a ventricular component will be added to the atrial mechanism. Thus, discerning the dominant mechanism in advanced stage TR remains challenging. Our study did not include RA remodeling parameters besides TA diameter and RA area. In addition, as the conservative and TTVR cohort were sampled during largely different time periods and as the standard of care may have changed during these periods, we cannot validly draw any conclusions from a comparison of events within atrial or non-atrial TR between conservative and TTVR treatments. Moreover, based on their baseline parameters, the 2 cohorts show major differences that render any matching approach to glean additional insight futile. However, the proposed atrial TR definition may be further validated in additional cohorts that may allow comparisons between conservative and TTVR treatments in either a case-control or matched analysis, or as a subgroup in a RCT. Parameters unaccounted for in our analysis may add additional validity to the atrial TR definition.

Conclusions

An atrial TR definition derived from advanced clustering strategies validated TV tenting height, RV diameter, and LVEF as atrial TR-associated parameters. Patients with atrial TR had lower rates of adverse outcome compared with non-atrial TR in conservatively treated patients with significant TR and after TTVR.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S2
Tables S1–S2

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