Improvement of the Prognosis Assessment of Severe Tricuspid Regurgitation by the Use of a Five-Grade Classification of Severity

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It is well known that some patients present with "more than severe" tricuspid regurgitation (TR). We aimed to assess the prognosis of these very severe TR patients. We defined very severe TR using 3 simple echocardiographic parameters: a coaptation gap≥10mm, a laminar TR flow and a systolic reversal of the hepatic vein flow. We included 259 consecutive patients (76 ± 13 years; 46% men) with moderate-to-severe TR (n = 114) and severe TR (n = 145). The primary end point was the combination of hospitalisation for right heart failure (RHF) and cardiovascular mortality. Median follow-up was 24(7 to 47) months. In patients with severe TR, 52 (36%) met the definition of very severe TR. These patients were younger, had more history of RHF and were more frequently treated with loop diuretics than those with moderate-to-severe TR (all p < 0.001). Four-year event-free survival rates were 68 ± 5%, for moderate-to-severe TR, 48 ± 6% for severe TR and only 35 ± 7% for very-severe TR (p < 0.001). On multivariable analysis, after adjustment for outcome predictors including age, comorbidity, RHF, TR etiology, left and right ventricular dysfunction, and tricuspid valve surgery, patients with very severe TR had a worsened prognosis than those with moderate-to-severe TR (Adjusted Hazard Ratio [95% Confidence Interval] = 2.43 [1.18 to 5.53]; p = 0.002) and than those with severe TR (Adjusted Hazard Ratio [95% Confidence Interval] = 2.23 [1.06 to 5.56]; p = 0.015). In conclusion, very severe TR is frequent in patients with severe TR, corresponds to a more advanced stage of the disease and is associated with poor outcomes. Therefore, the use of a 5-grade classification of TR severity is justified in routine clinical practice. (ID-RCB: 2017-A03233-50). **(Am J Cardiol 2020;132:119−125)**

Tricuspid regurgitation (TR) is common, affecting approximately 0.5% of the general population.[1,2] Although mild TR is benign, severe TR is consistently associated with a dismal prognosis[3−6] and even moderate TR could have substantial consequences.[7,8] Hence, the grading of TR by Doppler-echocardiography is crucial. Only a minority of patients with severe TR are referred for surgery[9,10] and the development of percutaneous techniques is eagerly awaited. According to recent trials, these devices provide improvements in functional status[11,12] with however a limited reduction of the regurgitation, which can still be severe after treatment.[11,12] Although current guidelines recommend to grade TR from mild to severe,[13,14] it is well known that TR can be "more than severe" and the currently used grading scheme for TR needs to be modified.[12,15] Hahn and Zamorano recently proposed a definition of massive and torrential TR using vena contracta and effective regurgitant orifice area (EROA) measurements.[16] However, although 4 grades are not sufficient to stratify TR patients, a 6-grade classification is difficult to apply and may not be relevant in daily clinical practice.[15] Therefore, we aimed to propose a "clinically relevant" definition of a fifth grade of TR (i.e., very severe TR), based on simple and reproducible parameters to better characterize this entity and to assess its prognostic value.

Methods

Between January 2013 and December 2018, 259 consecutive patients aged ≥18 years with a diagnosis of ≥ moderate-to-severe TR on echocardiography were identified and included in an electronic database.[5] Three distinct etiologies of TR were identified: primary (organic) TR (including drug-induced valve diseases, rheumatic valvular disease, myxomatous disease, infective endocarditis, carcinoid syndrome, congenital heart disease, traumatic and post-iatrogenic), secondary (functional) TR (to left-sided heart or pulmonary disease), and idiopathic TR defined by structurally normal tricuspid valves with no overt organic TR cause, no left-sided valvular heart disease, preserved left ventricular ejection fraction (LVEF) and no previous cardiac surgery.[2,4,5] Baseline clinical and demographic characteristics including age, gender, body mass index, and cardiovascular risk factors were collected. The Charlson

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See page 124 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.06.044

comorbidity index was calculated for each patient.[17] This study was approved by an independent ethics committee and was conducted in accordance with institutional policies, French legislation, and the revised Declaration of Helsinki (ID-RCB: 2017-A03233-50).

All patients underwent a comprehensive Doppler-echocardiographic assessment, using high-quality ultrasound systems (EPIQ 5 or EPIQ 7, Philips Healthcare). Two-dimensional digitalized videos and images were stored and analyzed offline (Xcelera, Philips Healthcare). Tricuspid valve morphology was evaluated by a multiview approach (parasternal long-axis, parasternal short-axis, apical 4-chamber, and subcostal views). TR was graded as moderate-to-severe (grade III) or severe (grade IV) according to guidelines by an integrative approach,[13,14] using semi quantitative (color flow jet area, vena contracta width, PISA radius, hepatic vein flow), and quantitative parameters (EROA, regurgitant volume).[13,14,18,19] To identify patients with "very severe" TR, each severe TR echocardiography was independently reviewed offline by 2 experienced operators. Very severe TR was defined by the combination of a coaptation gap of the tricuspid valve leaflets ≥10mm, a laminar TR flow and a systolic inversion of the hepatic vein flow (Figure 1). The coaptation gap was assessed using 2D echocardiography in end-systole in each available view to identify the largest coaptation defect. The gap size was measured at the tip of the leaflets. The laminar nature of the flow was defined as a dense, triangular, short-slope, with a peak in early systole corresponding to a rapid pressure equalization between the right atrium (RA) and the right ventricle, recorded in continuous Doppler. The systolic reversal of the hepatic vein flow was defined as a biphasic waveform with a single retrograde systolic wave and a single anterograde diastolic wave per cardiac cycle.[13,18]

RV assessment was based on multiple views and RV function was evaluated using the tricuspid annular plane systolic excursion (TAPSE) and the peak systolic velocity S' wave of the tricuspid annulus. RV dysfunction was defined by either TAPSE<14mm and/or S'<10cm/s.[20]

Median (interquartile range) follow-up was 24 (7 to 47) months. Most patients were followed by clinical consultations and echocardiography in the Amiens hospital outpatient clinic. A few patients were followed in public hospitals or private practices by referring cardiologists working in collaboration with our centre. All surviving patients were followed until the end of the study. Information on follow-up was retrospectively obtained by direct patient interview and clinical examination and/or repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. The composite primary end point was the combination of hospitalisation for right heart failure (RHF) and cardiovascular mortality. Clinical decisions on medical management or referral for surgery were made by the Heart Team with the approval of the patient's cardiologist based on the European Society of Cardiology's guidelines.

Data were analyzed using SPSS 25.0 (SPSS Inc. Chicago, IL). Continuous variables are expressed as the mean ± standard deviation and categorical variables as numbers and percentages. The relationship between baseline continuous variables and the various groups was explored by one-way analysis of variance. The chi-sqaure test was used to compare categorical variables between groups. The independent-sample *t* test or the Mann-Whitney U tests were used to compare continuous variables with normal or skewed distributions between groups. Event rates ± standard errors were estimated using the Kaplan-Meier method and compared by 2-sided log-rank tests. Multivariable analyses were performed using Cox proportional hazard

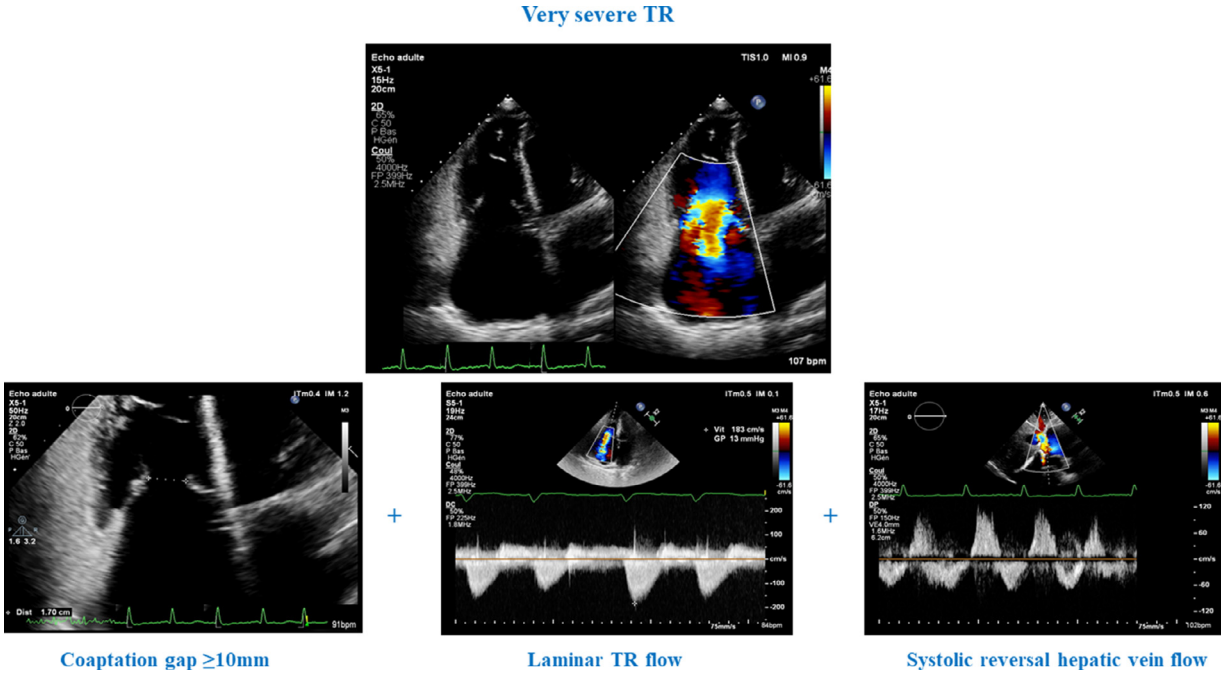

Figure 1. Definition of very severe tricuspid regurgitation in the study. TR = tricuspid regurgitation.

Table 1
Baseline demographic and clinical characteristics of patients according to tricuspid regurgitation severity

Variables	Tricuspid regurgitation			p value
	Moderate-to-severe (n = 114)	Severe (n = 93)	Very severe (n = 52)	
Age (years)	78 ± 12	73 ± 13†	74 ± 13†	<0.001
Men	45 (39%)	45 (48%)	29 (56%)	0.125
BMI (kg/m^2)	26 ± 4	27 ± 5	30 ± 9†	0.001
NYHA				
1−2	81 (71%)	58 (62%)	37 (71%)	0.353
3−4	30 (29%)	32 (37%)	11 (34%)	
RHF	50 (44%)	59 (63%)*	39 (75%) †	<0.001
Hypertension	88 (77%)	66 (71%)	36 (69%)	0.453
Diabetes mellitus	29 (25%)	26(28%)	13 (25%)	0.896
Dyslipidemia	54 (47%)	50 (54%)	19 (36%)	0.137
Charlson index	3.5 ± 2.1	3.1 ± 2.1	3.6 ± 2.3	0.296
Atrial fibrillation	77 (68%)	71 (76%)	39 (75%)	0.328
TR etiology				
Primary (organic) TR	15 (13%)	14 (15%)	9 (17%)	0.776
Secondary (functional) TR	56 (49%)	50 (54%)	25 (48%)	0.739
- Previous left valvular surgery	*24 (43%)*	*25 (50%)*	*9 (36%)*	
- Native mitral and/or aortic valve disease	*24 (43%)*	*19 (38%)*	*12 (48%)*	
- Systolic heart failure	*5 (9%)*	*4 (8%)*	*4 (16%)*	
- Pulmonary disease	*3 (5%)*	*2 (4%)*	*0 (0%)*	
Idiopathic TR	43 (38%)	29 (31%)	18 (35%)	0.617
Treatment				
ACE-I	31 (27%)	31 (33%)	17 (33%)	0.589
ARB	17 (15%)	15 (16%)	3 (6%)	0.182
Aldactone	14 (12%)	35 (38%)†	19 (36%)†	<0.001
Beta-blocker	84 (74%)	63 (68%)	37 (71%)	0.644
Loop diuretics	81 (71%)	81 (87%)*	48 (92%)†	0.001
Dose of loop diuretics (mg/day)	136 ± 230	149 ± 182	160 ± 207	0.809

Continuous variables are expressed as mean ±1 standard deviation and categorical variables are expressed as percentages and numbers.
* p <0.05 versus moderate-to-severe TR.
† p <0.001 versus moderate-to-severe TR.
Abbreviations: ACE- I= angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blockers; BMI = Body Mass Index; NYHA = New York Heart Association; RHF = right heart failure; TR = tricuspid regurgitation.

models. We entered covariates considered to have potential prognostic impact into the model on an epidemiological basis.[1,3,5] They were age, gender, body mass index, Charlson comorbidity index, New York Heart Association (NYHA) class, coronary artery disease, AF, history of RHF, creatinine clearance, dose of diuretics, TR etiology, LVEF and RV dysfunction. The effect of tricuspid valve surgery on outcome was analyzed as a time-dependent covariate using the entire duration of follow-up. To assess interobserver reproducibility, 2 investigators (FP and YB) analyzed a randomly chosen subset of 20 patients with severe TR. Interobserver reproducibility was evaluated using the Pearson correlation coefficient and intraclass correlation coefficient (ICC) for the coaptation gap and Cohen's Kappa statistics for the laminar character of the TR flow and inversion of hepatic vein flow. The limit of statistical significance was $p < 0.05$ and all tests were 2-tailed.

Results

The study population consisted of 259 patients: 114 with moderate-to-severe TR and 145 with severe TR. Interobserver reproducibility was good for the measurement of coaptation gap (r = 0.93; intraclass correlation coefficient = 0.96 [0.86 to 0.99]), and perfect for the determination of the laminar character of the TR flow (kappa = 1) and for the identification of an inverted hepatic vein flow (kappa = 1). In the 145 patients with severe TR, 52 met the definition of very severe TR with an agreement of 100% between the 2 operators.

Baseline demographic and clinical characteristics of the study population (mean age 76 ± 13 years; 46% men) according to the 3 groups of TR severity are displayed in Table 1. Overall, 38 patients (15%) had primary TR, 131 (50%) had secondary TR and 90 (35%) had idiopathic TR. One hundred and seventy-six patients (68%) were in NYHA stage I or II at the time of baseline echocardiography, and 148 patients (57%) had a history of RHF. Compared with patients with moderate-to-severe TR, patients with severe TR and patients with very severe TR were younger, had more history of RHF and were more frequently treated with loop diuretics and with Aldactone (Table 1). Patients with very severe TR had greater BMI than those with moderate-to-severe TR. There were no differences between groups in terms of gender, NYHA stage, hypertension, coronary artery disease, AF, Charlson comorbidity index or TR etiologies (Table 1).

Baseline echocardiographic variables according to TR severity are presented in Table 2. Patients with severe or very severe TR had larger left atrial and RA volumes, and

Table 2
Baseline echocardiographic characteristics of patients according to tricuspid regurgitation severity

Variables	Tricuspid regurgitation			p value
	Moderate-to-severe (n = 114)	Severe (n = 93)	Very severe (n = 52)	
Left-sided heart characteristics				
LV end diastolic diameter (mm)	50 ± 9	52 ± 9	50 ± 9	0.324
LV end systolic diameter (mm)	36 ± 9	38 ± 10	37 ± 9	0.297
LVEF (%)	55 ± 12	51 ± 14*	53 ± 11	0.047
Left atrial volume index (ml/m^2)	49 ± 21	58 ± 26*	59 ± 28*	0.024
Cardiac output (l/min)	4.8 ± 1.4	4.6 ± 1.4	4.8 ± 1.8	0.387
Right-sided heart characteristics				
TAPSE (mm)	18 ± 5	16 ± 5*	18 ± 6	0.044
S' wave (cm/sec)	10.7 ± 3.2	10.3 ± 3.7	10.2 ± 3.2	0.559
Fractional area change (%)	38 ± 10	34 ± 9	37 ± 10	0.060
Right atrial area (cm^2)	26 ± 8	32 ± 10*	38 ± 12*	<0.001
Right atrial volume (ml)	93 ± 52	127 ± 63*	159 ± 82†	<0.001
EROA of TR (mm^2)	28 ± 10	59 ± 24†	110 ± 63†	<0.001
Regurgitant volume (ml)	31 ± 10	53 ± 21†	74 ± 34†	<0.001
Vena contracta (mm)	6 ± 2	8 ± 2†	18 ± 3†	<0.001
Coaptation gap				
- *Presence*	8 (7%)	44 (47%) †	52 (100%) †	<0.001
- *Size if present (mm)*	1.8 ± 0.4	3.9 ± 1.6 †	15.1 ± 4.2 †	<0.001
Laminar flow	3.5 (4)	37.6 (35) †	100 (52) †	<0.001
hepatic vein flow reversal	24 (21%)	62 (67%) †	52 (100%) †	<0.001
IVC diameter (mm)	21.4 ± 4.7	26.0 ± 5.3†	29.6 ± 5.4†	<0.001
Peak jet velocity of TR (m/sec)	3.2 ± 0.6	2.8 ± 0.5†	2.1 ± 0.4†	<0.001
Tricuspid annulus diameter (mm)	42 ± 5	44 ± 5†	49 ± 7†	<0.001
RVOT proximal diameter (mm)	39 ± 6	44 ± 7*	47 ± 7†	<0.001
RV basal diameter (mm)	48 ± 7	51 ± 7*	54 ± 8†	<0.001

Continuous variables are expressed as mean ±1 standard deviation and categorical variables are expressed as percentages and numbers.
* $p < 0.05$ versus moderate-to-severe TR.
† $p < 0.001$ versus moderate-to-severe TR.
Abbreviations: EROA = effective regurgitant orifice area; IVC = inferior vena cava; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; RVOT = right ventricular outflow tract; TAPSE = Tricuspid Annular Plane Systolic Excursion; TR = tricuspid regurgitation.

greater tricuspid annulus, basal RV and inferior vena cava diameters than patients with moderate-to-severe TR (Table 2). Patients with severe TR had lower TAPSE than those with moderate-to-severe TR. There were no significant differences between groups in terms of S' wave and RV fractional area changes. As expected, the EROA, regurgitant volume, and vena contracta increased with TR severity whereas the peak jet velocity of TR decreased (Table 2).

During follow-up, 24 patients underwent tricuspid valve surgery: 6 (5%) with moderate-to-severe TR, 8 (9%) with severe TR, and 10 (20%) with very severe TR ($p = 0.014$). Ninety-three deaths (36%) were recorded during follow-up, 59 (63%) of which were cardiovascular-related, and 92 patients (35%) experienced at least 1 episode of RHF decompensation requiring hospitalization. Four-year event-free (cardiovascular death and hospitalization for RHF) survival rates were 68 ± 5% for patients with moderate-to-severe TR, 48 ± 6% for patients with severe TR, and 35 ± 7% for patients with very severe TR ($p < 0.001$) (Figure 2). On multivariable analysis, there were no differences in terms of event-free survival between patients with moderate-to-severe TR and those with severe TR (adjusted hazard ratio [HR] [95% confidence interval (CI)] = 1.14 [0.67 to 1.97], $p = 0.63$). However, patients with very severe TR had a worse prognosis than those with moderate-to-severe TR (adjusted HR [95% CI] = 2.33 [1.29 to 4.21], $p < 0.001$) or severe TR (adjusted HR [95% CI] = 1.98 [1.12 to 3.84],

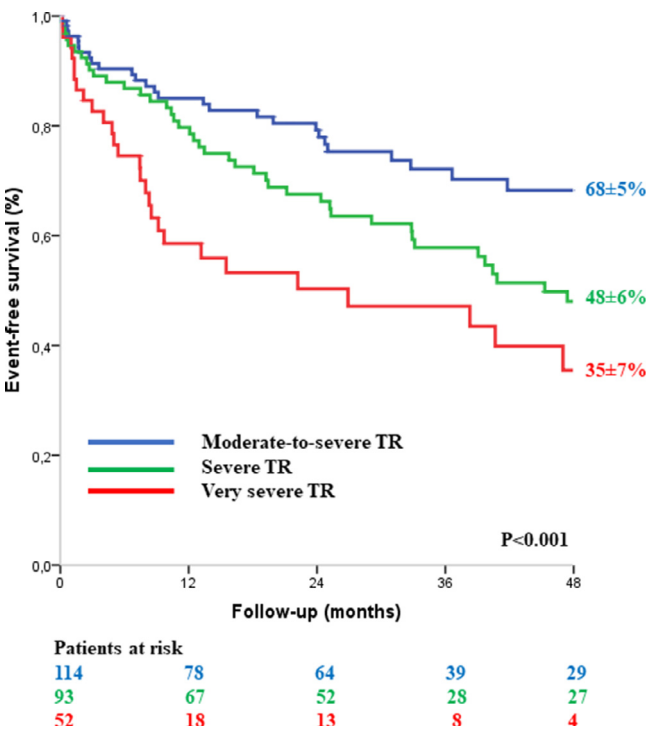

Figure 2. Kaplan Meier event-free survival curves according to tricuspid regurgitation severity. TR = tricuspid regurgitation.

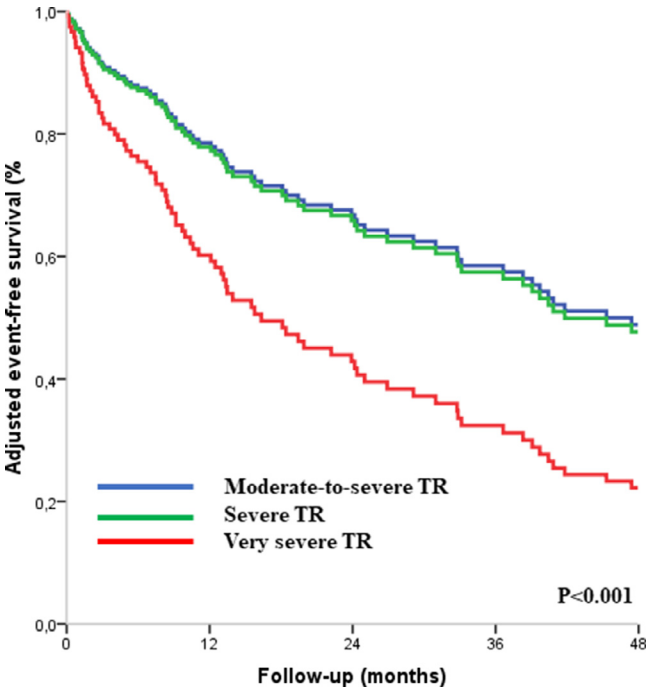

Figure 3. Cox adjusted event-free survival curves according to tricuspid regurgitation severity. TR = tricuspid regurgitation.

p = 0.005) (Figure 3) even after further adjustment for tricuspid valve surgery treated as a time-dependent variable (adjusted HR [95% CI] = 2.43 [1.18 to 5.53], p = 0.002 and adjusted HR [95% CI] = 2.23 [1.06 to 5.56], p = 0.015 respectively). Very severe TR remained associated with poorer outcomes after exclusion of patients with primary TR (adjusted HR [95% CI] = 2.39 [1.20 to 4.75], p = 0.013) and in the subset combining patients with secondary TR without severe left-sided disease (n = 75) and those with idiopathic TR (n = 90) (adjusted HR [95% CI] = 1.63 [1.02 to 2.87], p = 0.028).

Discussion

The results of the present study show that very severe TR is common in patients with severe TR (36%), regardless of TR etiology, and corresponds to a more advanced stage of the disease with more RHF, larger RA and RV and more severe RV dysfunction. Our definition of very severe TR (grade 5), based on 3 simple reproducible anatomic and hemodynamic parameters, allows easy identification of a subgroup of patients with a high risk of events. Indeed, after adjustment for established outcome predictors, very severe TR was associated with a more than 2-fold increase in the risk of hospitalization for RHF or death from cardiovascular causes.

Significant TR is consistently associated with poor outcomes with a direct relationship between the grade of the regurgitation and the risk of death.[3,5–8] In a previous study, we reported that patients with significant TR (≥grade III) exhibit relative survival of only 75% compared with the general population matched for age and sex.[5] In a cohort of 5,223 American veterans (mostly men), TR severity, was strongly correlated with survival at 4-years, all etiologies combined. After adjusting for age, inferior vena cava diameter, LVEF, and RV dilatation and dysfunction, mortality was greater for patients with moderate or severe TR than for the rest of the cohort.[3] In heart failure, functional TR is associated with excess mortality, increasing with the severity of TR.[7] Hence, the grading of TR by Doppler-echocardiography is crucial.

Tricuspid transcatheter therapies are raising great hopes for the treatment of severe TR. However, to date, these techniques appear to only reduce TR by approximately one half, often leaving a significant residual regurgitation.[11] Indeed, in the study by Hahn et al. [11] for example, the mean reduction in the EROA of TR was -0.22 ± 0.29 mm2 for a mean baseline EROA of 0.85 ± 0.22 mm2, resulting in a mean residual EROA of 0.63 ± 0.29 mm2.[11,16] Based on current guidelines,[13,14] these patients thus remained in the "severe" grade, with however, significant improvement in stroke volume and quality of life,[11,16] underscoring the need to rethink the quantification of severe TR. Accordingly, Hahn and Zamorano proposed in a remarkable editorial,[16] to add 2 additional degrees of severity to the actual grading scheme of TR: massive (grade 5) and torrential TR (grade 6). However, the suggested cut-off values for EROA and vena contracta to define massive and torrential TR were proposed without prognostic validation. Furthermore, although 4 grades are not sufficient for the risk stratification of TR, a 6-grade classification is difficult to apply and it may not be relevant in routine clinical practice to distinguish grade 6 from grade 5. Accordingly, Santoro et al. reported that patients with "more-than-severe TR" (>grade 4) had poorer outcomes than those with "only severe TR", with no difference between the massive and torrential forms when they tested this classification in terms of prognosis.[15]

EROA and vena contracta may not be the best parameters to distinguish among severe TR those with very severe TR. Indeed, these 2 quantitative methods are associated with poor interobserver agreement in mitral regurgitation,[21] and are more difficult to apply in TR due to the specific geometry of the valve.[22] In contrast to mitral or aortic regurgitation, the further subclassification of TR severity into 4 grades according to quantitative criteria has not been validated in the literature.[14] Indeed, although studies showed that an EROA of 40 mm^2 or greater[19] and a vena contracta > 7 mm[18] can be used to classify patients with severe TR, the values used to define mild, moderate, or severe TR are identical to those recommended for grading mitral regurgitation, despite the large differences between these 2 valves in terms of anatomy and hemodynamic conditions.[13,14,22] Furthermore, the use of conventional color Doppler quantitative parameters to grade TR is based on geometrical assumptions and the extrapolation of concepts that are true for primary mitral regurgitation but not necessarily so for TR, especially secondary severe restrictive TR. In this context, we propose a definition for very severe TR using a combination of 3 simple and reproducible parameters: a coaptation gap ≥ 10 mm, the laminar character of the TR flow, and a systolic reversal of the hepatic vein flow. Defined as such, very severe TR is common in patients with severe TR (36% in our series), corresponds to a more advanced stage of the disease with worse clinical and echocardiographic features and is associated

with a more than two-fold increase in the risk of RHF hospitalization or death from cardiovascular causes.

Our study has several limitations. Our study suffers from the inherent limitations of retrospective analyses. Because the study sample size is not very large (n = 259), it is difficult to draw conclusions on subgroup analyses. TAPSE and S' were used to define RV dysfunction. However, these parameters show limitations in the context of severe TR, especially in patients with previous cardiac surgery. Assessment of the severity of TR was performed on stored images acquired by different operators. However, all echocardiograms were conducted by experienced cardiologists in heart valve disease and reviewed by 2 independent operators.

In conclusion, we proposed 5-grade classification of TR using a simple definition of very severe TR (grade 5) by combining a coaptation gap ≥10mm with a laminar character of the TR flow and a systolic reversal of the hepatic vein flow. Very severe TR, as defined, is frequent in patients with severe TR, corresponds to a more advanced stage of the disease and is associated with poor outcomes. Further prospective multicenter studies are needed to validate our definition of very severe TR and confirm our findings.

Author contributions

The contribution of the authors is as follows:

Design of the study: Tribouilloy. Acquisition of data: All authors. Analysis and interpretation of data: Peugnet, Bohbot, Tribouilloy. Drafting of the manuscript: Peugnet, Bohbot, Tribouilloy. Critical revision for important intellectual content: all authors. Statistical analysis: Bohbot. Study supervision: Tribouilloy.

Disclosure

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this paper.

Uncited Reference'

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