Natural Course of Nonsevere Secondary Tricuspid Regurgitation

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Background: Secondary tricuspid regurgitation (sTR) is frequent in patients with heart failure with reduced ejection fraction and is associated with adverse outcomes despite guideline-directed therapy. However, little is known about the natural course of nonsevere sTR and its relation to cardiac remodeling and outcomes. The aims of this study were therefore to investigate the natural course of sTR progression using quantitative measurements, to assess the prognostic impact on long-term mortality, and to identify risk factors associated with progressive sTR.

Methods: A total of 216 patients with heart failure with reduced ejection fraction receiving guideline-directed therapy were included in this long-term observational study. Progression of sTR was quantitatively defined as an increase of 0.2 cm^2 in effective regurgitant orifice area or 15 mL in regurgitant volume, with transition to at least moderate sTR. Kaplan-Meier and Cox regression analyses were applied to assess survival during a 5-year follow-up period.

Results: Among patients with nonsevere sTR at baseline, 62 (29%) experienced sTR progression. Progressive sTR was accompanied by larger left and right atrial volumes ($P = .02$ and $P < .02$, respectively) and a higher prevalence of atrial fibrillation ($P < .04$). During a median follow-up period of 60 months (interquartile range, 37–60 months), 82 patients died. Progression of sTR conveyed a higher risk for long-term mortality (hazard ratio, 1.77; 95% CI, 1.1–2.83; $P < .02$), even after multivariate adjustment for bootstrap-selected (adjusted hazard ratio, 1.70; 95% CI, 1.06–2.74; $P < .03$) and clinical confounder (adjusted hazard ratio, 1.80; 95% CI, 1.07–3.05; $P < .03$) models.

Conclusions: The incidence of progressive sTR despite guideline-directed therapy is associated with adverse cardiac and valvular remodeling as well as a significantly higher long-term mortality. Biatrial enlargement as well as atrial fibrillation are associated with the development of subsequent progressive sTR and may help identify patients at risk for sTR progression, potentially creating a window of opportunity for closer follow-up and newly arising minimally invasive transcatheter repair therapies. (J Am Soc Echocardiogr 2021;34:13-9.)

Keywords: Secondary tricuspid regurgitation, Heart failure with reduced ejection fraction, Progressive tricuspid regurgitation, Effective regurgitant orifice area, Regurgitant volume

Secondary tricuspid regurgitation (sTR) is a common valvular lesion in patients with heart failure with reduced ejection fraction (HFrEF), affecting up to 70% of these patients. The presence of moderate or greater sTR is independently related to mortality despite optimized guideline directed therapy (GDT).[1-3] sTR occurs because of structural alterations of myocardial and annular geometry.[4] In the presence of left heart disease, increasing left atrial (LA) size and pressure further promote right atrial (RA) and tricuspid annular (TA) dilatation, resulting in a flattening of the saddle-shaped tricuspid annulus, thereby inducing leaflet tethering.[5,6] The sTR-induced volume overload subsequently drives further TA and ventricular remodeling, leading to sTR progression, thus becoming a driving factor of the disease.[7] It has been a common belief that functional sTR in the presence of left heart disease would resolve by treating the latter,[8] but previous results demonstrated that untreated concomitant sTR is independently

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Abbreviations

AF = Atrial fibrillation

EROA = Effective regurgitant orifice area

GDT = Guideline-directed therapy

HFrEF = Heart failure with reduced ejection fraction

HR = Hazard ratio

IQR = Interquartile range

LA = Left atrial

LV = Left ventricular

NYHA = New York Heart Association

OR = Odds ratio

PASP = Pulmonary artery systolic pressure

PH = Pulmonary hypertension

PM = Pacemaker

RA = Right atrial

RVol = Regurgitant volume

RV = Right ventricular

sTR = Secondary tricuspid regurgitation

TA = Tricuspid annular

TR = Tricuspid regurgitation

TV = Tricuspid valve

associated with symptom burden, and even a modest increase in sTR volume translates to a sustained rise in mortality.[1,3,9] A closer understanding regarding pathophysiology and disease progression is needed to guide future interventional recommendations in sTR, as data on the evolution of this disorder in patients with heart failure receiving optimized GDT remain scarce.

Therefore, we aimed to assess the natural course of sTR progression or regression under GDT and investigated its prognostic impact on long-term mortality in patients with HFrEF. Moreover, we sought to identify functional and morphologic differences related to sTR progression and to establish associated risk factors.

METHODS

Study Population

Patients with HFrEF at the heart failure outpatient clinic of Vienna General Hospital, a university-affiliated tertiary care center, were included in this observational, noninterventional study from January 2004 to June 2012. HFrEF was defined as a history of heart failure symptoms and history of left ventricular (LV) ejection fraction $< 40\%$ according to the latest heart failure guidelines.[10] All patients underwent comprehensive transthoracic echocardiographic examinations at study inclusion and additional transthoracic echocardiographic examinations within 3 years thereafter. In an attempt to define a clinically relevant increase in nonsevere sTR, we defined sTR progression as an advance of at least one grade in severity corresponding to an increase of 0.2 cm^2 in effective regurgitant orifice area (EROA) or 15 mL in regurgitant volume (RVol),[11] with transition to at least moderate sTR. Similarly, regression was defined as a decrease of 0.2 cm^2 in EROA or of 15 mL in RVol. Patients with primary tricuspid regurgitation (TR) were excluded. The study was approved by the ethics committee of the Medical University of Vienna.

Echocardiographic Assessment

We used commercially available equipment to perform baseline and follow-up echocardiography (Vivid 5 and Vivid 7; GE Healthcare, Little Chalfont, United Kingdom). We measured LV and right ventricular (RV) diameters as well as RA volume from a standard four-chamber view. LV and LA volumes were assessed using the disk summation algorithm in standard four- and two-chamber views, and LV ejection fraction was calculated using the biplane Simpson method. Semiquantitative assessment of LV and RV function was performed by experienced echocardiographers using multiple imaging windows and graded as normal, mild, mild to moderate, moderate, moderate to severe, or severe. TR was graded using an integrated approach[11] and quantified using the proximal isovelocity surface area method. According to the respective guidelines, we graded valvular stenosis and regurgitation in an integrated manner as mild, mild to moderate, moderate, moderate to severe, or severe.[11] Pulmonary artery systolic pressure (PASP) was calculated by adding RA pressure, estimated by assessing inferior vena cava size and collapsibility, to the peak systolic gradient of the TR signal by continuous-wave spectral Doppler.[12] Intra- and interobserver variability for EROA and RVol were assessed in 20 randomly selected patients as previously described.[1] Interobserver agreement and intraobserver consistency were tested using intraclass correlation coefficients.

Statistical Analysis

Discrete data are presented as count (percentage) and were compared by using the χ^2 test. Continuous data are presented as median (interquartile range [IQR]) and were analyzed using the Kruskal-Wallis test. Odds ratios (ORs) associated with sTR progression were estimated using a univariate logistic regression analysis. To assess the effect of sTR progression on survival, we applied Cox proportional-hazard regression analysis. We formed a confounder cluster encompassing age, sex, body mass index, ischemic etiology of heart failure, New York Heart Association (NYHA) functional class, hypertension, diabetes, creatinine, LV end-diastolic diameter, LV function, LA diameter, RV end-diastolic diameter, RV function, RA diameter, renin angiotensin system antagonists, β-blockers, mineralocorticoid antagonist therapy, and intracardiac pacemaker leads to account for potential confounding effects. We used a stepwise bootstrap resampling procedure including all aforementioned variables to identify best fitting variables for the final multivariate Cox regression model. Five hundred repeats with a P value of .05 for selection were performed, and variables selected in 80% of all repeats were included in the final confounder model (i.e., age and creatinine). Additionally, a clinical confounder model comprising LV ejection fraction, RV function, NYHA functional class, and etiology of heart failure was used to adjust for potential confounding effects. We tested and satisfied the proportional hazards assumption in all cases using Schoenfeld residuals. Interactions between all variables included in the multivariate model and sTR progression were tested by entering interaction terms into the Cox proportional-hazard regression models. To assess time-dependent discriminative power of TR progression, we applied the Kaplan-Meier analysis (log-rank test). Two-sided P values $< .05$ were considered to indicate statistical significance. SPSS version 24.0 (IBM, Armonk, NY) and Stata version 11 (StataCorp, College Station, TX) were used for all statistical analyses.

RESULTS

Baseline Characteristics

Two hundred sixteen patients with HFrEF were included in this study; the median age was 69 years (IQR, 63–76 years), and 167 patients (77%) were men. The median N-terminal pro–brain natriuretic peptide level was 3,575 pg/mL (IQR, 1,782–7,827 pg/mL) at index; 38% of patients were in NYHA functional class III and 16% in

HIGHLIGHTS

- Doppler echocardiographic measurements facilitate the definition of progressive TR.
- One third of patients with HFrEF with nonsevere TR experience sTR progression.
- sTR progression is associated with adverse remodeling and worse outcome despite GDT.

NYHA functional class IV. Eighty-seven percent of patients ($n = 187$) received renin-angiotensin system antagonists, 181 patients (84%) were treated with β-blockers, 122 patients (56%) received mineralocorticoid receptor antagonists, and 127 patients (59%) received diuretic therapy. Detailed baseline characteristics of the entire study population are shown in Supplemental Table 1. Of the entire study population, 171 patients (79%) presented with mild sTR, 23 patients (11%) with moderate sTR, and 22 patients (10%) with severe sTR. Detailed information regarding the evolution of sTR from baseline to follow-up are displayed in Figure 1. The median time from baseline echocardiography to the follow-up study was 12 months (IQR, 4–22 months). TR EROA and RVol showed good reproducibility, with intraclass correlation coefficients > 0.95 when tested for interobserver and intraobserver variability.

Evolution of sTR

Among patients with nonsevere sTR at baseline, 129 (60%) remained stable, whereas 62 patients (29%) experienced sTR progression within 3 years after study inclusion. In contrast, nine patients (4%) in the entire study population experienced sTR regression. Of those, six patients showed regression from severe sTR at baseline, while the remaining three patients did regress from moderate to mild sTR and were counted as stable for the survival analysis comparing patients with stable nonsevere sTR, progressive sTR, and severe sTR at baseline. The median time from baseline echocardiography to the study showing progression was 12 months (IQR, 4–22 months). Supplemental Table 1 provides detailed baseline characteristics according to sTR progression. Briefly, patients with subsequent progression of sTR were more symptomatic at baseline (NYHA functional class IV 18% vs 9%, $P < .01$) and had larger atrial size at baseline (median LA volume index, 46 mL/m^2 [IQR, 36–58 mL/m^2] in patients with stable nonsevere sTR vs 53 mL/m^2 [IQR, 41–75 mL/m^2] in patients with progressive sTR [$P < .05$]; median RA volume, 65 mL [IQR, 44–89 mL] in patients with stable nonsevere sTR vs 77 mL [IQR, 58–103 mL] in patients with progressive sTR [$P = .03$]). No differences were observed in medical and device therapies between patients with subsequent progressive sTR and those with stable nonsevere sTR.

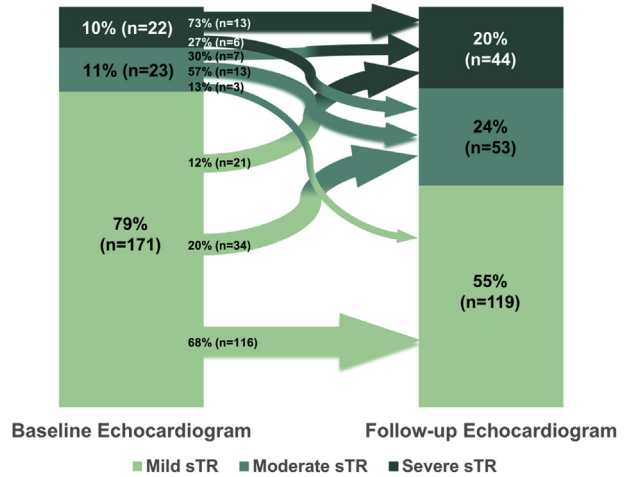


Figure 1 Longitudinal evolution of sTR from baseline to follow-up echocardiographic examinations.

Baseline Parameters Associated with Progressive sTR

In the univariate logistic regression analysis, both LA and RA size at baseline were significantly associated with progressive sTR. LA volume was associated with sTR progression, with an OR for a 1-SD increase of 1.50 (95% CI, 1.06–2.13; $P = .02$), and RA volume, with an OR for a 1-SD increase of 1.56 (95% CI, 1.08–2.25; $P < .02$). Furthermore, the presence of atrial fibrillation (AF) was associated with sTR progression, with an OR of 1.99 (95% CI, 1.04–3.81; $P < .04$). Interestingly, the presence of cardiac leads (i.e., pacemaker or automatic implantable cardioverter-defibrillator) was not significantly associated with TR progression, which might be influenced by the high prevalence of RV leads in this population, as the majority of patients had indications for automatic implantable cardioverter-defibrillator placement. Detailed results of the univariate logistic regression analysis are displayed in Table 1.

Progressive sTR: Associated Morphologic and Functional Maladaptation

Echocardiography follow-up measurements within 3 years after study inclusion are presented in Table 2. At follow-up, patients with sTR progression showed more dilated right ventricles (median basal RV end-diastolic diameter, 39 mm [IQR, 34–46 mm] vs 43 mm [IQR, 37–50 mm]; $P < .04$], larger atrial size (median LA volume, 76 mL [IQR, 54–105 mL] vs 90 mL [IQR, 68–120 mL] [$P = .01$]; median RA volume, 55 mL [IQR, 40–77 mL] vs 71 mL [IQR, 46–98] [$P < .01$]), and had higher estimated PASP (median, 42 mm Hg [IQR, 33–55 mm Hg] vs 51 mm Hg [IQR, 41–63 mm Hg]; $P < .01$). Furthermore, TA diameter index differed significantly between the two groups at follow-up, with a median of 20.1 mm/m^2 (IQR, 17.8–22.3 mm/m^2) in patients with stable nonsevere sTR compared with 21.6 mm/m^2 [IQR, 18.8–24.1 mm/m^2) in those with progressive sTR ($P < .02$).

Progression of sTR and Outcomes

During a median follow-up period of 60 months (IQR, 37–60 months) starting from baseline echocardiography, 82 patients died. Within 3 years of the index examination, sTR progression was associated with significant long-term mortality in the crude Cox regression analysis with a hazard ratio (HR) of 1.77 (95% CI, 1.1–2.83; $P < .02$). The results remained virtually unchanged after multivariate adjustment for our bootstrap-selected confounder model, with an adjusted HR of 1.70 (95% CI, 1.06–2.74; $P = .03$) as well as our clinical confounder model (encompassing ischemic etiology of heart failure, NYHA functional class, LV function, and RV function), with an adjusted HR of 1.80 (95% CI, 1.07–3.05; $P < .03$), and no significant collinearity was detected in our multivariate models. Kaplan-Meier analysis demonstrated a significant increase of long-term mortality in patients with progressive sTR compared

with those with stable nonsevere sTR (log-rank $P < .03$) comparable with patients with severe sTR at baseline (Figure 2). Moreover, the Kaplan-Meier curves seem to show similar time to event-rate rates in the first years in patients with stable nonsevere sTR and those with subsequent progressive sTR and a deviation of the curves thereafter, illustrating a potential time frame to change the course of the disease. In contrast, regression of sTR occurred in nine patients (4%) but was not associated with a beneficial effect on survival (crude HR, 1.08; 95% CI, 0.55–2.14; $P = .81$).

DISCUSSION

Expanding our previous results investigating the natural history of sTR, in the present study we focused on the course of sTR over time using a quantitative definition of progressive sTR. Our data show that one third of patients with nonsevere sTR experience progression of sTR within the first 3 years of follow-up despite optimized GDT. sTR progression was associated with a poor prognosis, even after careful adjustment for bootstrap-adjusted and echocardiographic confounder clusters. In patients subsequently developing progressive sTR, we observed a higher prevalence of AF and larger atrial volumes at baseline. At follow-up, sTR progression was related to more severe RV and biatrial enlargement, as well as increased pulmonary pressures. Interestingly, regression of sTR did not change prognosis. However, this result must be interpreted with caution, as the number of regressors in the study was small.

Table 1 Univariate logistic regression analysis assessing risk factors at baseline for sTR progression

Variables	SD	OR (95% CI)	*P*
Baseline characteristics			
Age	11	0.97 (0.72–1.32)	.86
Sex, male	—	0.92 (0.45–1.87)	.82
BMI	—	0.96 (0.70–1.30)	.78
Ischemic etiology of HF	—	0.96 (0.50–1.84)	.90
Hypertension	—	0.91 (0.47–1.74)	.77
Diabetes	—	1.72 (0.88–3.38)	.11
AF	—	1.99 (1.04–3.81)	<.04*
NYHA functional class	—	0.77 (0.57–1.05)	.10
Creatinine	1.04	1.06 (0.79–1.43)	.69
Echocardiographic characteristics			
LV end-diastolic diameter	9	1.09 (0.81–1.47)	.58
LV ejection fraction	9	1.17 (0.85–1.60)	.34
RV end-diastolic diameter	8	1.35 (0.96–1.88)	.08
RV function	—	1.28 (0.95–1.73)	.10
LA volume	44	1.50 (1.06–2.13)	.02*
LA volume index	21	1.53 (1.07–2.18)	.02*
RA volume	45	1.56 (1.08–2.25)	<.02*
TR peak velocity	0.6	1.25 (0.90–1.74)	.18
PASP	17	1.30 (0.95–1.80)	.10
Mitral regurgitation	—	0.69 (0.32–1.45)	.33
TA diameter index	4.9	1.27 (0.92–1.74)	.14
Medications			
RAS antagonist	—	0.63 (0.21–1.86)	.40
β-blockers	—	0.79 (0.30–2.10)	.64
Mineralocorticoid antagonist	—	1.31 (0.68–2.52)	.41
Cardiac devices			
AICD	—	0.57 (0.21–1.59)	.29
Pacemaker	—	1.62 (0.81–3.24)	.17

AICD, Automatic implantable cardioverter-defibrillator; *BMI*, body mass index; *HF*, heart failure; *RAS*, renin-angiotensin system.
*Statistically significant.

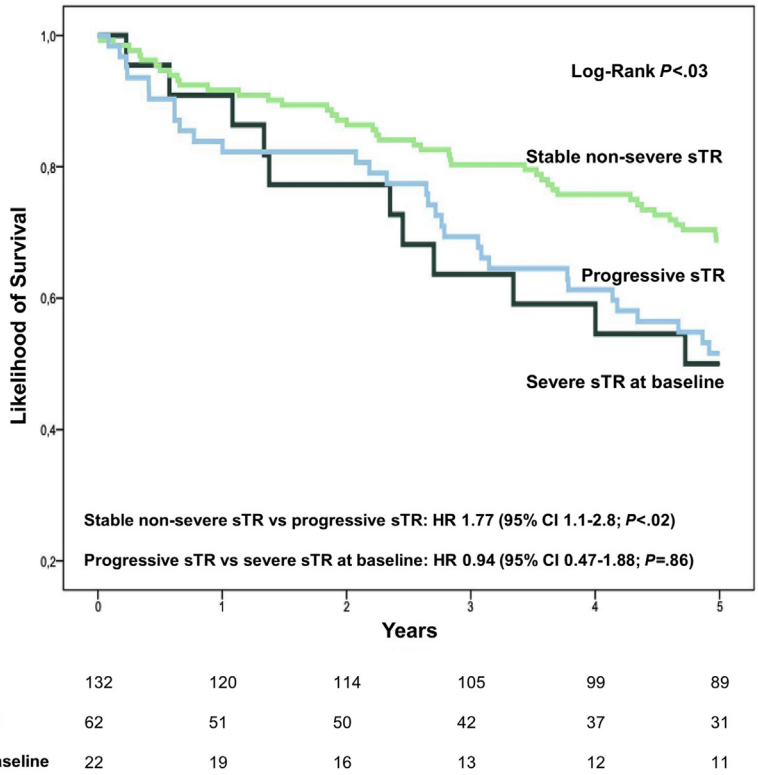
Current Clinical Practice in TR

Treatment options for sTR are limited, and medical therapy consists mainly of diuretic therapy to reduce peripheral edema and symptom

Table 2 Echocardiographic characteristics at baseline and follow-up

Echocardiographic characteristics	sTR stable nonsevere (*n* = 132)	sTR progression (*n* = 62)	*P*
Baseline examination			
LV end-diastolic diameter, mm	60 (55–66)	60 (55–65)	.77
LA volume, mL	88 (70–111)	100 (76–142)	<.05*
LA volume index, mL/m^2	46 (36–58)	53 (41–75)	<.05*
RA volume, mL	65 (44–89)	77.5 (58–103)	.03*
Basal RV end-diastolic diameter, mm	38 (34–43)	39 (33–46)	.09
PASP, mm Hg	47 (36–59)	52 (39–62)	.12
Mitral regurgitation (moderate or greater)	82 (62)	37 (60)	.75
TA diameter, mm	33 (28–39.3)	34.3 (27.5–40.9)	.36
TA diameter index, mm/m^2	16.5 (14.3–20.9)	17.4 (14.3–21.9)	.23
Follow-up examination			
LV end-diastolic diameter, mm	59 (53–66)	62 (53–69)	.38
LA volume, mL	76 (54–105)	90 (68–120)	.01*
LA volume index, mL/m^2	41 (28–52)	48 (35–63)	<.01*
RA volume, mL	55 (40–77)	71 (46–98)	<.01*
Basal RV end-diastolic diameter, mm	39.5 (34–46)	43 (37–50)	<.04*
PASP, mm Hg	42 (33–55)	51 (41–63)	<.01*
Mitral regurgitation (moderate or greater)	56 (42)	30 (48)	.75
TA diameter, mm	39.2 (34–43)	39.75 (34.6–46)	.14
TA diameter index, mm/m^2	20.1 (17.8–22.3)	21.6 (18.8–24.1)	<.02*

Data are expressed as median (IQR) or as number (percentage).
*Statistically significant.



Number at risk						
Stable sTR	132	120	114	105	99	89
Progressive sTR	62	51	50	42	37	31
Severe sTR at baseline	22	19	16	13	12	11

Figure 2 Kaplan-Meier estimates of long-term mortality comparing patients with stable nonsevere sTR with patients with progressive sTR and severe sTR at baseline (log-rank $P < .03$).

burden or targeting the underlying left-sided myocardial impairment with guideline-directed heart failure therapy. Isolated tricuspid repair remains the valve surgery with the highest mortality and is restricted to highly symptomatic patients with progressive RV dilatation or worsening of function.[13] Although recent guidelines for valvular heart disease define progressive TR as a distinct entity, the definition considers mostly patients undergoing left-sided heart surgery and is not tailored to heart failure cohorts.[14] TA dilatation is a strong prognostic factor for the development of late severe sTR, and tricuspid annuloplasty is therefore performed concomitantly if TA dilatation > 40 mm is present. The current data add new insight by showing that in patients with heart failure, sTR progression occurs even in patients with only mild or moderate sTR at baseline, within 3 years of follow-up, despite GDT and independent of baseline TA. This is true for approximately one third of patients with HFrEF and nonsevere sTR, who are seemingly identifiable by a combination of clinical and echocardiographic variables, in whom it might be reasonable to consider adding tricuspid valve (TV) annuloplasty to another cardiac procedure to prevent sTR progression. Moreover, as transcatheter interventions showed promising results for the mitral valve,[15] new transcatheter treatment options for the TV have arisen and are currently under study,[16] possibly representing a new, less invasive treatment option that does not require left-sided heart surgery in the future and could thus be performed earlier.

Quantitative Approach to Assess sTR

Quantitative analysis of TR consists of the proximal flow convergence method, comprising EROA and RVol. There are fewer validation studies of this method available for TR than for mitral and aortic regurgitation.[17,18] However, the current guidelines for the assessment of valvular regurgitation recommend an integrated approach for TR grading, also including quantitative measurements.[11] Moreover, we recently demonstrated that minor increases in quantitative parameters of sTR are associated with excess mortality.[1] Inspired by these results, we present a quantitative definition of progressive sTR characterized by an increase of 0.2 cm^2 in EROA or 15 mL in RVol, with transition to at least moderate sTR. Furthermore, our data highlight that this increase in quantitative parameters of sTR assessment is associated with significant adverse outcomes.

Risk Factors and Morphologic Maladaptation Associated with Progression of sTR

So far, risk factors for the progression of sTR have been assessed in only a few studies. Medvedofsky *et al.*[19] investigated progressive TR in the setting of concomitant pulmonary hypertension (PH) and identified further increases in PASP, increase in RV size, and decrease in TV coverage as determinants for progressive TR. Furthermore, AF has been suggested as a significant offender in TR progression in a study population with predominant heart failure with preserved ejection fraction.[20] Recent data in an unselected TR study population added, among others, age, presence of a cardiac device lead, reduced RV systolic function, and increased TA diameter as independent risk factors for the development of TR progression.[2]

The present study revealed risk factors for the progression of sTR in a contemporary cohort of patients with HFrEF receiving GDT, namely, biatrial enlargement as well as the presence of AF, in line

with previous results in unselected patient cohorts.[21,22] Biatrial enlargement potentially promotes AF and TA dilatation, thereby stimulating sTR progression. Moreover, neither PASP nor direct TV morphology were associated with sTR progression in our HFrEF population. Importantly, previous studies reported inconsistent results concerning determinants associated with TR progression.[20] Secondary PH exerts increased afterload on the right ventricle, thus causing dilatation and tethering of the TV apparatus, which leads to sTR. In our cohort of only patients with HFrEF, we did not see differences in PASP and RV size at baseline between patients with stable nonsevere sTR and those subsequently developing sTR progression. It is possible that these specific variables do not represent the initial driving force of sTR in HFrEF. This is supported by previous results highlighting that although PH is strongly associated with TR, not all patients with PH develop sTR.[4] Correspondingly, we observed significant differences in RV size and PASP at the follow-up echocardiographic examination. Also, TA diameter index, in comparison with the measurement at baseline, was significantly higher in patients with sTR progression. Altogether, our results indicate that the combination of AF and biatrial enlargement is a major offender for the development of progressive sTR. Establishing a cluster of variables possibly able to identify patients at significant risk early enables the appealing possibility to alter the clinical course of the disease, especially in light of new developing transcatheter repair techniques.

Progressive TR and Outcomes

The adverse outcomes associated with moderate or severe sTR have been widely demonstrated.[3,21,22] However, the dynamic nature of sTR progression in patients with mild or moderate sTR at baseline has not been investigated. Our results strongly emphasize the significance of progressive sTR, namely, a roughly 1.8-fold risk for mortality, even after careful adjustment for bootstrap-adjusted and clinical confounder clusters. Furthermore, there was no difference regarding the risk for mortality between patients with severe sTR at baseline and those with subsequent sTR progression. Therefore, our results strengthen the notion that progressive sTR despite GDT is associated with an excess risk for mortality comparable with patients with severe sTR and therefore represents an entity that may potentially benefit from more aggressive treatment strategies before sTR fuels heart failure progression to late stages of the disease.

The majority of the current data originate from post–left-sided valve surgery studies and research in different patient cohorts.[2,19,20,23,24] Interestingly, a recent study fueled this discussion in showing that sTR was not associated with increased cardiovascular risk if left heart disease was present.[25] In contrast, an investigation of patients with heart failure with preserved ejection fraction and PH demonstrated a significant association of more than moderate sTR with excess mortality.[26] In accordance, Prihadi *et al.*[2] recently associated TR progression with adverse outcome and underlined the significant association of the time to development of progressive TR. However, the population of their study was heterogenous, with only one fifth of their patients having left heart disease. Our data provide information on sTR evolution exclusively in patients with HFrEF receiving GDT, in which even the presence of moderate or greater sTR at baseline is exceedingly high.[1] Moreover, these patients are often deemed unsuitable for surgical options and therefore represent the population primarily targeted by newly arising minimally invasive therapies.

Regression of sTR

Our results indicate that a small proportion of patients with severe sTR at baseline experience regression of sTR with GDT. Nonetheless, this regression was not associated with an improved prognosis compared with patients with stable nonsevere sTR. Medvedofsky *et al.*[19] demonstrated a significant association among sTR regression, RV reverse remodeling, morphologic TV parameters, and outcomes. However, their study considered only patients with PH. Other studies demonstrated that once TA dilatation as well as RV remodeling and impaired function are present, the process of sTR is progressive and drives heart failure.[27,28] Our data might support those findings, suggesting that once severe sTR fueled heart failure to progress toward late stages of the disease, sTR regression alone might not be able to reverse this process. However, these conclusions need to be interpreted with caution given the small number of regressors included in this study.

Limitations

The results of this study represent the experience of a single tertiary care center. However, this guarantees a homogenous patient population, compliant to a coherent clinical routine and undergoing echocardiographic examinations with consistent quality. Additionally, these data illustrate the natural course of sTR in the specific cohort of patients with HFrEF and are thus hypothesis generating for the evolution of sTR and the identification of patients at risk for sTR progression in this group. Although we did not assess fluid overload potentially influencing load-dependent sTR, all included patients were recruited and treated at our outpatient heart failure clinic, so cardiac decompensation at the time of the examination can be ruled out.

CONCLUSION

Our results reveal that one third of patients with HFrEF experience sTR progression despite GDT, which is associated with adverse structural remodeling and translates into significantly worse outcomes. Additionally, we described specific risk factors associated with sTR progression, which may help identify patients at risk in an early stage of the disease. This enables the possibility for closer follow-up and timely intervention, especially in light of newly arising transcatheter repair techniques, which will hopefully be able to reduce the burden of sTR.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2020.08.018.

REFERENCES

1. Bartko PE, Arfsten H, Frey MK, Heitzinger G, Pavo N, Cho A, et al. Natural history of functional tricuspid regurgitation: implications of quantitative Doppler assessment. JACC Cardiovasc Imaging 2019;12:389-97.
2. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. Eur Heart J 2018;39:3574-81.
3. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405-9.

4. Badano LP, Muraru D, Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. Eur Heart J 2013;34:1875-85.
5. Ton-Nu TT, Levine RA, Handschumacher MD, Dorer DJ, Yosefy C, Fan D, et al. Geometric determinants of functional tricuspid regurgitation: insights from 3-dimensional echocardiography. Circulation 2006;114:143-9.
6. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. J Am Coll Cardiol 2009;53:401-8.
7. Fukuda S, Song JM, Gillinov AM, McCarthy PM, Daimon M, Kongsaerepong V, et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. Circulation 2005;111:975-9.
8. Braunwald NS, Ross J Jr., Morrow AG. Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement. Circulation 1967;35:163-9.
9. Goldstone AB, Howard JL, Cohen JE, MacArthur JW Jr., Atluri P, Kirkpatrick JN, et al. Natural history of coexistent tricuspid regurgitation in patients with degenerative mitral valve disease: implications for future guidelines. J Thorac Cardiovasc Surg 2014;148:2802-9.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.
11. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303-71.
12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.
13. Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, et al. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation 2011;123:1929-39.
14. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
15. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307-18.
16. Nickenig G, Weber M, Schueler R, Hausleiter J, Nabauer M, von Bardeleben RS, et al. 6-Month outcomes of tricuspid valve reconstruction for patients with severe tricuspid regurgitation. J Am Coll Cardiol 2019;73:1905-15.
17. Grossmann G, Stein M, Kochs M, Hoher M, Koenig W, Hombach V, et al. Comparison of the proximal flow convergence method and the jet area method for the assessment of the severity of tricuspid regurgitation. Eur Heart J 1998;19:652-9.
18. Tribouilloy CM, Enriquez-Sarano M, Capps MA, Bailey KR, Tajik AJ. Contrasting effect of similar effective regurgitant orifice area in mitral and tricuspid regurgitation: a quantitative Doppler echocardiographic study. J Am Soc Echocardiogr 2002;15:958-65.
19. Medvedofsky D, Aronson D, Gomberg-Maitland M, Thomeas V, Rich S, Spencer K, et al. Tricuspid regurgitation progression and regression in pulmonary arterial hypertension: implications for right ventricular and tricuspid valve apparatus geometry and patients outcome. Eur Heart J Cardiovasc Imaging 2017;18:86-94.
20. Shiran A, Najjar R, Adawi S, Aronson D. Risk factors for progression of functional tricuspid regurgitation. Am J Cardiol 2014;113:995-1000.
21. Hung J, Koelling T, Semigran MJ, Dec GW, Levine RA, Di Salvo TG. Usefulness of echocardiographic determined tricuspid regurgitation in predicting event-free survival in severe heart failure secondary to idiopathic-dilated cardiomyopathy or to ischemic cardiomyopathy. Am J Cardiol 1998;82:1301-3.
22. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J 2002;144:524-9.
23. Matsuyama K, Matsumoto M, Sugita T, Nishizawa J, Tokuda Y, Matsuo T. Predictors of residual tricuspid regurgitation after mitral valve surgery. Ann Thorac Surg 2003;75:1826-8.
24. Wang G, Sun Z, Xia J, Deng Y, Chen J, Su G, et al. Predictors of secondary tricuspid regurgitation after left-sided valve replacement. Surg Today 2008;38:778-83.
25. Mutlak D, Khoury E, Lessick J, Kehat I, Agmon Y, Aronson D. Lack of increased cardiovascular risk due to functional tricuspid regurgitation in patients with left-sided heart disease. J Am Soc Echocardiogr 2019;32:1538-46.e1.
26. Bar N, Schwartz LA, Biner S, Aviram G, Ingbir M, Nachmany I, et al. Clinical outcome of isolated tricuspid regurgitation in patients with preserved left ventricular ejection fraction and pulmonary hypertension. J Am Soc Echocardiogr 2018;31:34-41.
27. Colombo T, Russo C, Ciliberto GR, Lanfranconi M, Bruschi G, Agati S, et al. Tricuspid regurgitation secondary to mitral valve disease: tricuspid annulus function as guide to tricuspid valve repair. Cardiovasc Surg 2001;9:369-77.
28. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg 2005;79:127-32.