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Original research

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ABSTRACT

Objective Severe secondary tricuspid regurgitation (STR) causes significant right atrial (RA) volume overload, resulting in structural and functional RA-remodelling. This study evaluated whether patients with severe STR and reduced RA function, as assessed by RA-reservoir-strain (RASr), show lower long-term prognosis.

Methods Consecutive patients, from a single centre, with first diagnosis of severe STR and RASr measure available, were included. Extensive echocardiographic analysis comprised measures of cardiac chamber size and function, assessed also by two-dimensional speckle-tracking strain analysis. Primary outcome was all-cause mortality, analysed from inclusion until death or last follow-up. The association of RASr with the outcome was evaluated by Cox regression analysis and Akaike information criterion.

Results A total of 586 patients with severe STR (age 68±13 years; 52% male) were included. Patients presented with mild right ventricular (RV) dilatation (end-diastolic area 13.8±6.5 cm^2/m^2) and dysfunction (free-wall strain 16.2±7.2%), and with moderate-to-severe RA dilatation (max area 15.0±5.3 cm^2/m^2); the median value of RASr was 13%. In the overall population, 10-year overall survival was low (40%, 349 deaths), and was significantly lower in patients with lower RASr (defined by the median value): 36% (195 deaths) for RASr ≤13% compared with 45% (154 deaths) for RASr >13% (log-rank p=0.016). With a median follow-up of 6.6 years, RASr was independently associated with all-cause mortality (HR per 5% RASr increase:0.928; 95% CI 0.864 to 0.996; p=0.038), providing additional value over relevant clinical and echocardiographic covariates (including RA size and RV function/size).

Conclusions Patients with severe STR presented with significant RA remodelling, and lower RA function, as measured by RASr, was independently associated with all-cause mortality, potentially improving risk stratification in these patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a need to optimise the risk stratification of patients diagnosed with significant tricuspid regurgitation (TR), since these patients are often referred for tricuspid valve (TV) intervention at a late stage with signs and symptoms of right-sided heart failure, which translates to high in-hospital mortality.

WHAT THIS STUDY ADDS

⇒ The current study shows, in patients with severe secondary tricuspid regurgitation (STR), that right atrial (RA) remodelling precedes right ventricular remodelling; the latter currently being used to guide the decision making in the management of TR.

⇒ Moreover, patients with lower RA function presented with significantly lower overall survival.

⇒ In order to improve patient care and allow timely referral for TV intervention, the evaluation of TR severity and TR aetiology should include a comprehensive assessment of RA size and RA function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The role of RA size and RA function in risk-stratification of patients with severe STR should be further tested in larger and multicentre studies and potentially in patients undergoing TR interventions, in order to confirm their potential use in clinical practice.

⇒ In the current study only two-dimensional echocardiography was used, while RA size might be better assessed by three-dimensional echocardiography, considering the complex and dynamic three-dimensional shape of the RA and TV annulus.

⇒ Whether RA function has a superior prognostic value to RA size in these patients should therefore be confirmed in future prospective studies.

INTRODUCTION

Despite the important role of the right atrium (RA) in the pathophysiology of tricuspid regurgitation (TR),[1 2] no studies have been published on the prognostic value of the RA in patients with severe TR. The 2021 European Society of Cardiology guidelines on valvular heart disease still recommend only the measurement of RA dimensions (along with the tricuspid valve (TV) annulus, right ventricular (RV) dimensions and function) for the evaluation and management of patients with severe TR, without in-depth analysis of RA remodelling or functional assessment.[3]

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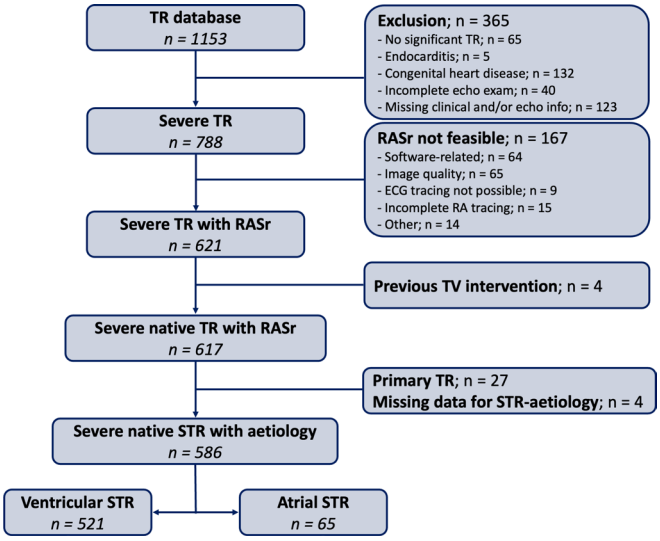


Figure 1 Flow chart for study population selection. STR, secondary tricuspid regurgitation; RA, right atrium; RASr, speckle-tracking strain analysis of the RA during the reservoir-phase; TR, tricuspid regurgitation; TV, tricuspid valve.

Accordingly, the aims of the current study were to evaluate in a large cohort of patients with severe secondary tricuspid regurgitation (STR) (1): Which baseline clinical and echocardiographic variables are associated with RA function, using two-dimensional speckle-tracking strain analysis of the RA during the reservoir-phase (RASr); and(2) The association of RASr with long-term all-cause mortality, independently of known prognostic factors, and whether it could improve risk-stratification.

METHODS

Study population

Consecutive patients first diagnosed with severe TR between 2006 and 2011, at the outpatient clinic or during hospitalisation in the Leiden University Medical Centre (Leiden, The Netherlands) were identified. Patients with active endocarditis, congenital heart disease, missing relevant clinical data or inadequate echocardiographic acoustic window were excluded from the current analysis. In addition, patients with prior TV intervention, patients in whom RASr-measurement was not feasible and patients diagnosed with primary TR or where STR aetiology (atrial vs ventricular) was not determinable, were also excluded (figure 1).

Demographic and clinical data were retrospectively collected from the departmental Cardiology Information System (EPD-Vision, Leiden, The Netherlands).

Clinical and echocardiographic variables

Baseline demographic, clinical, laboratory and echocardiographic variables were evaluated at the time of first diagnosis of severe STR. Clinical characteristics included risk factors for cardiovascular disease, relevant medical history and comorbidities, functional status (New York Heart Association (NYHA) functional class) and medication use.

Transthoracic echocardiograms were performed at rest using available equipment (Vivid7-E9-E95 systems, GE-Vingmed, Horten, Norway) and images were digitally stored for offline analysis (EchoPAC version 113.0.3-202-203-204; GE-Vingmed, Horten, Norway). Per protocol, for patients in atrial fibrillation (AF), for each image, three beats were acquired and averaged. M-mode, two-dimensional and colour, continuous-wave and pulsed-wave Doppler-data were acquired, according to current guidelines.[4–6] From the apical four-chamber and two-chamber views, left ventricular (LV) volumes were measured, and LV ejection fraction was quantified using the biplane Simpson's method.[4] Left atrial maximum volume was measured at end systole using the biplane method.[4] Left-sided valvular disease was evaluated through a multiparametrical approach and defined as significant in the presence of at least moderate-to-severe mitral regurgitation or moderate aortic stenosis. RV measurements were performed on the RV-focused apical view. RV end-systolic and end-diastolic areas were traced, and the RV fractional area change was derived. Additionally, RV function was evaluated by tricuspid annular plane systolic excursion and RV free-wall longitudinal strain, measured by two-dimensional speckle-tracking echocardiography. RA maximum area was measured at end systole on the RV-focused apical view. Furthermore, integrative assessment of TR severity was performed using a multiparametrical approach and subsequently graded according to current guidelines.[5 6] TR severity grading was primarily performed using quantitative parameters. When inconclusive results were found, semiquantitative and subsequent qualitative parameters were used to make a distinction between severe or moderate TR; the last ones excluded from the analysis. Systolic pulmonary artery pressure was estimated from peak TR velocity, applying the Bernoulli equation and adding RA pressure.[4] Furthermore, STR aetiology was classified into atrial STR or ventricular STR, using a stepwise approach based on clinical and echocardiographic characteristics as proposed in the recent recommendations[7] and described in previous publications.[8]

Two-dimensional speckle-tracking echocardiographic analysis

The assessment of RA strain by two-dimensional speckle-tracking echocardiography was performed offline using EchoPAC V.203 software (GE-Vingmed), applying the software for left atrial strain on the RA, on a RV-focused apical view, according to current guidelines (figure 2).[9] The onset of the QRS complex (defining LV end diastole) was selected as the zero reference point (R–R gating). The RA endocardial wall was traced manually and the region of interest was defined by the software and then manually adjusted to cover the entire RA myocardium. Next, the myocardium was divided into six segments by the software. RA strain was defined as the average of the peak values during the cardiac cycle of all six segments.[9] The resulting RA strain curve is shown in figure 2. RASr was chosen over RA strain during the conduit or contractile phase, because RASr reflects atrial compliance and can still be assessed in patients with AF.

Follow-up and outcomes definition

The primary endpoint of the study was all-cause mortality. Outcomes were analysed from the time of first diagnosis of significant STR until death or last follow-up in April 2022. Survival data were ascertained from the departmental Cardiology Information System and the Social Security Death Index and were complete for all patients.

Statistical analysis

Continuous variables are presented as mean±SD when normally distributed or as median and IQR when non-normally distributed. Categorical variables are presented as frequencies and percentages. Differences between the two groups of RASr were compared using the independent-samples Student's t-test,

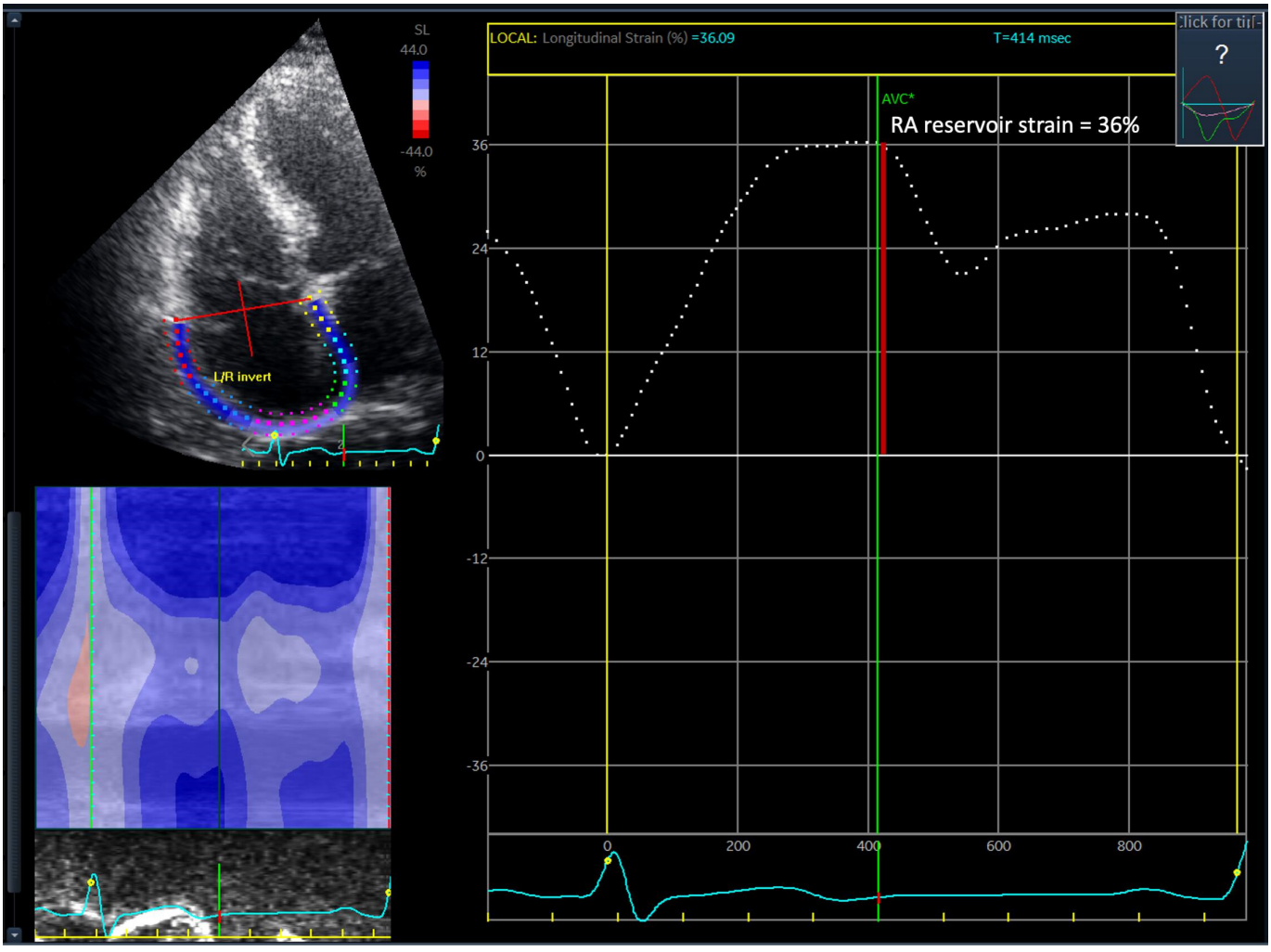


Figure 2 Measurement of RASr by two-dimensional speckle-tracking echocardiography. The region of interest is illustrated in the upper left quadrant covering the right atrial myocardium. The average RASr from the six RA myocardial segments is displayed by the dotted white curve in the right figure. The resulting RA-strain curve provided two peaks with the first peak just before TV opening, representing RASr and the second peak representing RA strain during the contraction phase (when in sinus rhythm). RA strain during the conduit phase is the difference between RASr and RA strain during the contraction phase. In this case, the RASr was 36% (red line). AVC, aortic valve closure; RA, right atrium; RASr, speckle-tracking strain analysis of the RA during the reservoir-phase; TV, tricuspid valve.

Mann-Whitney U test, Pearson's χ^2 test or Fisher's exact test, as appropriate.

In order to evaluate the impact of RASr in patients with severe STR, the study population was divided into two groups. Since there are currently no validated reference RASr values available in patients diagnosed with severe STR, the population was divided according to the median RASr value.

Multivariable linear regression analysis was performed to identify the independent correlates of RASr. Goodness of fit is expressed as the unadjusted R^2. Multicollinearity was checked by means of variance inflation factor analysis, with none of the variables included presenting a variance inflation factor >2.5.

The Kaplan-Meier survival analysis was used to estimate 10-year survival rates, and differences between groups were analysed using the log-rank test. To investigate the association between clinical and echocardiographic factors with all-cause mortality, univariable and multivariable Cox proportional hazards regression analyses were performed. Significant variables on the univariable analysis ($p<0.05$), together with AF (a recognised parameter associated with RA remodelling[10]), were included in the multivariable Cox regression analysis. Multicollinearity for the continuous variables was assessed by variance inflation factor analysis in addition to correlation factor analysis (correlation coefficient >0.60). Additionally, spline curve analysis was performed to visualise the relation between the hazard of all-cause mortality and RASr (online supplemental figure 1). Akaike information criterion (AIC) was used to distinguish among a set of possible models, testing different RA/RV variables, and selecting the best-fit model associated with outcome. The baseline model included all covariates on the multivariable Cox regression analysis, adding RA/RV size/function parameters to this model in a different order, using a stepwise approach.

Twenty individuals were selected randomly for the evaluation of intraobserver and interobserver variability of RASr. Excellent agreement was defined by an intraclass correlation coefficient >0.90, whereas good agreement was defined by a value between 0.75 and 0.90. Values of two-sided $p<0.05$ were considered statistically significant. All data were analysed using SPSS for Windows, V.25.0 (IBM Corp, Armonk, New York, USA) and R V.1.4.1717 (R-Foundation for Statistical Computing, Vienna, Austria).

Table 1 Baseline characteristics of the overall population and according to RASr values, split by a median of 13%

Clinical characteristics	Overall population n=586	RASr ≤13% n=304	RASr >13% n=282	P value	Missing data n (%)
Age, years	68±13	69±13	67±14	0.100	0 (0)
Male sex, n (%)	305 (52)	172 (57)	133 (47)	**0.025**	0 (0)
Body mass index, kg/m^2	25.5±4.4	26.0±4.6	25.1±4.1	**0.009**	12 (2)
Arterial hypertension, n (%)	449 (80)	249 (85)	200 (74)	**0.001**	22 (4)
Diabetes mellitus, n (%)	110 (20)	63 (22)	47 (17)	0.242	21 (4)
Dyslipidaemia, n (%)	261 (48)	142 (50)	119 (47)	0.492	45 (8)
Smoking, n (%)	162 (30)	89 (31)	73 (29)	0.572	48 (8)
Coronary artery disease, n (%)	252 (43)	139 (46)	113 (41)	0.209	4[1]
Atrial fibrillation, n (%)	322 (55)	219 (72)	103 (37)	**<0.001**	0 (0)
Chronic kidney disease, n (%)	86 (15)	49 (16)	37 (14)	0.351	15 (3)
COPD, n (%)	86 (15)	52 (18)	34 (13)	0.101	21 (4)
NYHA functional class >II, n (%)	255 (46)	152 (53)	103 (39)	**0.002**	34 (6)
CIED lead present, n (%)	199 (34)	114 (38)	85 (30)	0.066	3[1]
Haemoglobin, g/L	126±20	126±20	127±21	0.666	40 (7)
Beta-blocker, n (%)	345 (65)	183 (65)	162 (64)	0.928	51 (9)
RAAS-inh, n (%)	345 (64)	191 (67)	154 (61)	0.149	50 (9)
Loop diuretic, n (%)	329 (58)	208 (70)	121 (45)	**<0.001**	18 (3)
MRA, n (%)	125 (23)	83 (29)	42 (17)	**0.001**	50 (9)

Values are mean±SD, median (IQR), or n (%).
CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAAS-inh, Renin-angiotensin-aldosterone system inhibitors; RASr, speckle-tracking strain analysis of the RA during the reservoir-phase.

RESULTS

Clinical and echocardiographic characteristics

A total of 586 patients diagnosed with severe STR were included in the current analysis. Clinical and echocardiographic characteristics of the overall population are presented in tables 1 and 2, respectively. Mean age was 68±13 years, with 305 (52%) male. Approximately half of the population had (paroxysmal/permanent) AF (55%) and were moderately symptomatic with NYHA functional class >II (46%). More than half of the population (58%) was treated with loop diuretics. Overall, patients showed mild RV dilatation and RV dysfunction, and moderate-to-severe RA dilatation. Patients presented with significantly reduced RASr, as a measure of RA function, with a median RASr value of 13% (IQR: 7%–22%). Data on RA conduit/contractile-strain for patients in sinus rhythm are available in online supplemental tables 1,2. Of note, 11% of patients were classified as atrial STR, with distinct differences in clinical as well as echocardiographic phenotype of these patients (online supplemental tables 3,4).

Furthermore, patients were divided in two groups according to the median RASr value (13%) and compared. Patients with

Table 2 Echocardiographic characteristics of the overall population and according to RASr values, split by a median of 13%

Echocardiographic characteristics	Overall population n=586	RASr ≤13% n=304	RASr >13% n=282	P value	Missing data n (%)
LV end-diastolic volume—indexed, ml/m^2	63.0 (44.5–91.6)	63.1 (46.5–95.4)	62.2 (43.3–90.1)	0.460	17 (3)
LV ejection fraction, %	43.9±15.5	40.7±15.2	47.2±15.2	**<0.001**	1 (0)
Left atrial volume max—indexed, ml/m^2	49.8 (35.7–68.4)	55.1 (40.1–75.4)	43.5 (31.7–59.6)	**<0.001**	37 (6)
Significant left-sided valvular disease, n (%)	269 (46)	147 (48)	122 (43)	0.245	0 (0)
Tricuspid valve annulus diameter, mm	42.4±7.9	44.1±7.7	40.5±7.6	**<0.001**	1 (0)
RV basal diameter, mm	46.7±8.4	48.4±8.4	44.7±8.0	**<0.001**	1 (0)
RV mid diameter, mm	35.7±8.6	36.5±8.7	34.8±8.4	**0.013**	3[1]
RV length, mm	72.8±12.7	74.6±13.2	70.9±12.0	**<0.001**	3[1]
RV end-diastolic area—indexed, cm^2/m^2	13.8±6.5	14.3±5.7	13.2±7.3	**0.042**	14 (2)
RV end-systolic area—indexed, cm^2/m^2	9.1±5.0	9.6±3.9	8.6±5.9	**0.010**	14 (2)
RV fractional area change, %	34.4±12.7	32.8±12.5	36.1±12.7	**0.002**	2 (0)
TAPSE, mm	15.5±5.0	13.6±4.0	17.6±5.1	**<0.001**	2 (0)
RV free-wall longitudinal-strain, %	16.2±7.2	13.7±6.2	18.9±7.3	**<0.001**	30 (5)
Right atrial area max—indexed, cm^2/m^2	15.0±5.3	16.4±6.0	13.5±4.0	**<0.001**	12 (2)
Systolic pulmonary artery pressure, mm Hg	44.6±17.0	44.5±15.8	44.7±18.2	0.860	22 (4)
RASr, %	13 (7–22)	8[3–8]	22 (16–28)	**<0.001**	
Atrial STR aetiology, n (%)	65 (11)	20 (7)	45 (16)	**<0.001**	0 (0)

Values are mean±SD, median (IQR), or n (%).
LV, left ventricle; RASr, speckle-tracking strain analysis of the RA during the reservoir-phase; RV, right ventricle; STR, secondary tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Multivariable linear regression analysis to identify parameters associated with RASr

Variables	Multivariable linear regression analysis	
	Unstandardised B (95%CI)	**P value**
Age, per 10 years	0.159 (–0.510 to 0.828)	0.641
Sex, male	0.253 (–1.478 to 1.985)	0.774
Arterial hypertension	1.484 (–3.665 to 0.697)	0.182
Diabetes mellitus	0.080 (–2.228 to 2.067)	0.941
Atrial fibrillation	5.555 (–7.350 to –3.759)	**<0.001**
Chronic kidney disease	0.760 (–1.589 to 3.108)	0.525
Chronic obstructive pulmonary disease	2.465 (–4.758 to –0.173)	**0.035**
NYHA functional class >II	1.055 (–2.786 to 0.676)	0.232
CIED lead present	0.964 (–0.820 to 2.747)	0.289
Haemoglobin, g/L	0.007 (–0.049 to 0.035)	0.744
Loop diuretic	3.394 (–5.307 to –1.481)	**0.001**
Left ventricular ejection fraction, per 10%	0.767 (0.164 to 1.371)	**0.013**
Left atrial volume max—indexed, per 5 mL/m^2	0.002 (–0.166 to 0.169)	0.986
RV end-diastolic area—indexed, per 5 cm2/m^2	0.075 (–0.937 to 0.788)	0.865
RV free-wall longitudinal strain, per 5%	2.650 (2.024 to 3.276)	**<0.001**
Right atrial area max—indexed, per 5 cm^2/m^2	2.442 (–3.415 to –1.468)	**<0.001**
Systolic pulmonary arterial pressure, per 5 mm Hg	0.205 (–0.052 to 0.460)	0.117
Atrial STR aetiology	0.871 (–2.036 to 3.779)	0.556

CIED, cardiac implantable electronic device; NYHA, New York Heart Association; RASr, speckle-tracking strain analysis of the RA during the reservoir-phase; RV, right ventricle; STR, secondary tricuspid regurgitation.

RASr ≤13% were more likely to be male, and more frequently diagnosed with AF. These patients were also more often symptomatic and were treated more frequently with diuretics. When comparing the left-sided echocardiographic variables, patients with RASr ≤13% had significantly lower LV ejection fraction and larger left atrial volumes. Regarding the right-sided echocardiographic variables, patients with RASr ≤13% had significantly larger RV and RA dimensions and worse RV systolic function. However, no significant differences were observed for systolic pulmonary artery pressure, when comparing patients according to the median RASr value. Additionally, patients with RASr ≤13% had more ventricular STR phenotype as compared with patients with RASr >13%.

Association of baseline variables with RASr

Multivariable linear regression analysis, evaluating the covariates associated with RASr in patients with severe STR, is shown in table 3. Better LV and RV systolic function (evaluated by LV ejection fraction and RV free-wall longitudinal strain, respectively) were significantly associated with higher RASr, whereas the presence of AF, chronic obstructive pulmonary disease (COPD), more pronounced heart failure symptoms (expressed by more frequent use of loop diuretics) and larger RA maximum area were significantly associated with lower RASr. The overall model showed an unadjusted R^2=0.429. Of note, STR aetiology was significantly correlated with RASr on the univariable linear regression analysis. However, atrial STR and ventricular STR present as distinct clinical and echocardiographic phenotypes. Consequently, patients with atrial STR presented with significantly higher RASr as compared with patients with ventricular STR (median RASr 22% (11%–28)% and 12% (7%–20)%, respectively), however, significant differences in RA dimension as well as RV size/function were also noted between the two distinct STR aetiologies (online supplemental tables 3,4). Hence, after correcting for these variables in the multivariable linear regression analysis, STR aetiology was no longer correlated with RASr.

Association of RASr with all-cause mortality

During a median follow-up of 79 (IQR: 19–147) months, 372 (64%) deaths occurred. The cumulative overall survival rates for the total population at 1-year, 5-year and 10-year follow-ups were 78%, 55% and 40%, respectively. The Kaplan-Meier curves for 10-year overall survival according to the RASr-median value are shown in figure 3. Survival rates at 10-year follow-ups were significantly lower in patients who presented lower RASr: 36% for patients with RASr ≤13% vs 45% for patients with RASr >13% (log-rank χ^2: 5.774; p=0.016).

Multivariable Cox regression analysis for all-cause mortality is presented in table 4 and showed that RASr >13% remained independently associated with outcome (HR per 5% RASr increase: 0.928 (95% CI 0.864 to 0.996)). Furthermore, age, body mass index, coronary artery disease, AF, chronic kidney disease, NYHA functional class >II, RV end-diastolic area, RV free-wall longitudinal strain and STR aetiology were also independently associated with all-cause mortality.

Figure 4 shows the AIC values for the baseline model, adding RA/RV size/function parameters to this model in a different order. The lowest AIC value was found for the baseline model including RV function (assessed by RV free-wall longitudinal strain), RV size (assessed by RV end-diastolic area indexed) and RA function (assessed by RASr). Adding RA size (assessed by RA maximum area) did not change the AIC value.

Reproducibility

The intraobserver and interobserver reproducibility of RASr measurements are summarised in online supplemental tables 5,6. The intraobserver and interobserver variability showed both excellent agreement with intraclas correlation coefficients of 0.981 (95% CI 0.950 to 0.992) and 0.993 (95% CI 0.981 to 0.997), respectively.

DISCUSSION

The main findings of the present study are threefold: (1) Patients diagnosed with severe STR presented with mild RV remodelling, but already advanced RA remodelling, including moderate-to-severe RA dilatation and moderate-to-severe RA dysfunction; (2) In these patients, AF, COPD, more pronounced heart failure symptoms, worse LV and RV systolic function, as well as RA dimensions were significantly associated with lower RASr; and (3) Patients with lower RA function (RASr ≤13%) had a lower survival rate, and RASr was independently associated with all-cause mortality with significant independent correlation, over relevant clinical and echocardiographic characteristics, including RA size as well as RV size and RV function.

RA remodelling in severe STR

The RV and TV annulus have been the main focus of interest in the assessment of TR, since STR is caused by TV annular dilatation and leaflet tethering secondary to RV dilatation.[7] In contrast, RA remodelling has received considerably less attention, despite its important role in the pathophysiology of TR, often preceding RV remodelling.[1 11 12] Guta *et al* showed that

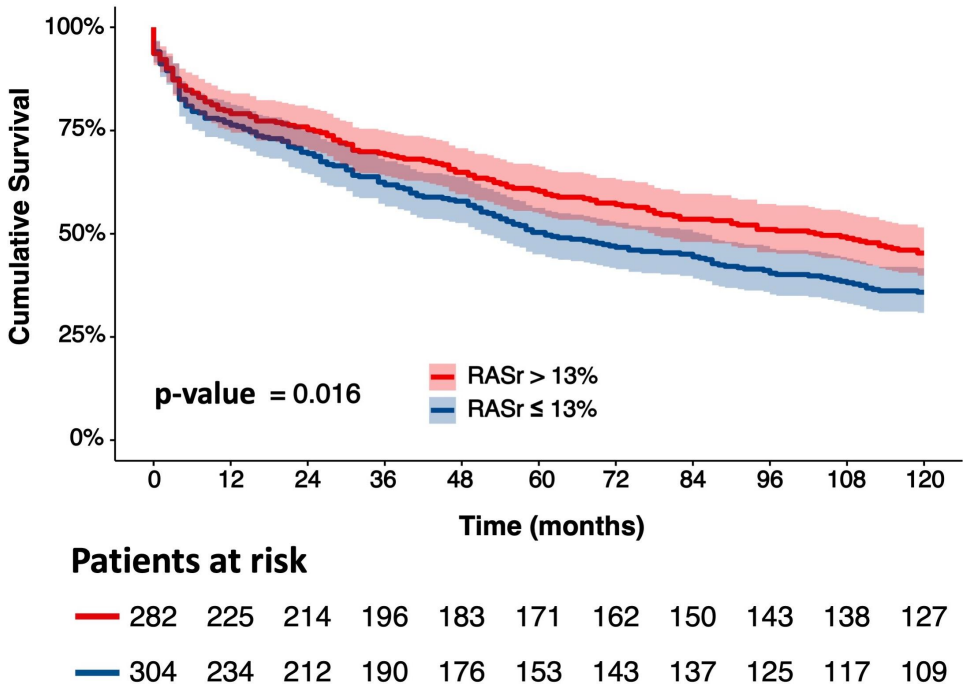


Figure 3 Overall survival according to the median cut-off of RASr. Kaplan-Meier curves showing a significantly lower 10-year overall survival in patients who presented with lower RASr (RASr ≤13%). RASr, speckle-tracking strain analysis of the RA during the reservoir-phase.

already 93% of patients with STR and AF presented with RA dilatation, whereas only 27% and 12% presented with, respectively, RV dilatation or RV dysfunction. Additionally, Harada *et al* explored RA remodelling in a small cohort of 69 patients with significant TR, showing that 78% had RA dilatation, whereas only 32% had RV dilatation.[13] The results of the current study, including 586 patients with severe STR, confirm these findings, showing that RA enlargement was more prevalent than RV dilatation and/or RV dysfunction.

Table 4 Multivariable Cox proportional hazard models for all-cause mortality in patients with severe STR

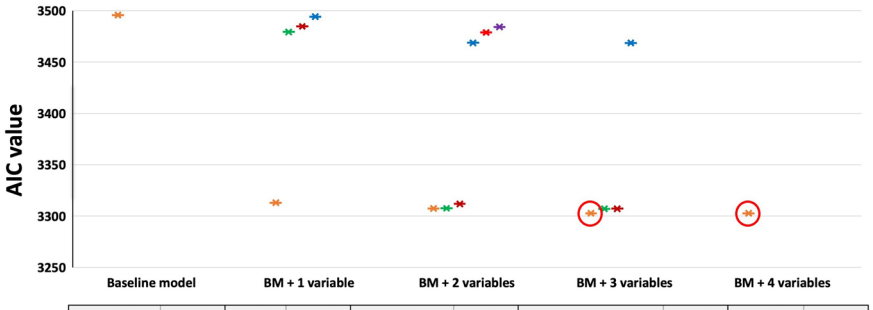
Variable	HR (95%CI)	P value
Age, per 10 years	1.347 (1.197 to 1.515)	**<0.001**
Sex, male	1.099 (0.856 to 1.412)	0.458
Body mass index, per 5 kg/m^2	0.831 (0.708 to 0.976)	**0.024**
Coronary artery disease	1.528 (1.187 to 1.966)	**0.001**
Atrial fibrillation	0.762 (0.581 to 0.998)	**0.048**
Chronic kidney disease	1.643 (1.207 to 2.236)	**0.002**
Chronic obstructive pulmonary disease	1.255 (0.930 to 1.694)	0.137
NYHA functional class >II	1.775 (1.380 to 2.284)	**<0.001**
CIED lead present	1.272 (0.989 to 1.636)	0.061
Loop diuretic	1.103 (0.819 to 1.486)	0.520
Mineralocorticoid receptor antagonist	0.809 (0.604 to 1.083)	0.154
Left ventricular ejection fraction, per 10%	1.074 (0.982 to 1.174)	0.117
Significant left-sided valvular disease	1.192 (0.933 to 1.522)	0.159
RV end-diastolic area—indexed, per 5 cm^2/m^2	1.109 (1.017 to 1.209)	**0.020**
RV free-wall longitudinal-strain, per 5%	0.902 (0.821 to 0.992)	**0.033**
Right atrial area max—indexed, per 5 cm^2/m^2	1.010 (0.899 to 1.135)	0.866
Systolic pulmonary arterial pressure, per 5 mm Hg	1.014 (0.979 to 1.050)	0.453
STR aetiology, ventricular versus atrial	1.787 (1.066 to 2.997)	**0.028**
RASr, per 5%	0.928 (0.864 to 0.996)	**0.038**

CIED, cardiac implantable electronic device; NYHA, New York Heart Association; RASr, speckle-tracking strain analysis of the RA during the reservoir-phase; RV, right ventricle; STR, secondary tricuspid regurgitation.

Furthermore, previous studies showed that RA size is associated with TV annular dilatation, independently from left-sided heart disease, and identified RA enlargement as the main determinant of TV annular dilatation and TR severity.[1 11 12 14] Normal reference ranges for the clinical assessment of RA function using two-dimensional speckle-tracking echocardiography in healthy subjects have been published, showing an average RASr of 44% (95% CI 25% to 63%).[15] Recently, Hinojar *et al*[16] assessed RA function in a small cohort of patients diagnosed with severe TR. They showed that patients with severe TR presented with significantly reduced RASr (median RASr 11.2% (7%–16)%), similar to the current study. Furthermore, in a multivariable linear regression analysis, in addition to RV function and larger RA size (both significantly associated with RASr in the study by Hinojar *et al*[16]), AF, heart failure symptoms (use of loop diuretics) and worse LV function were also significantly related to lower RA function.

Overall survival in severe STR and association with RA remodelling

The prognosis of patients with severe STR has been reported in several studies, with 1-year and 5-year overall survival rates around 70% and 45%, respectively,[17–21] which are comparable to the ones observed in the current study. This low survival rate is to be interpreted partially in relation with the associated important comorbidities (including left-sided heart failure, and coronary artery disease, COPD, etc[17–20]) observed in these patients. Also importantly, at the time of inclusion of these studies, percutaneous TV interventions were not yet widely available and the treating physicians were reluctant to refer these patients for surgery. These patients were therefore left untreated and developed relatively advanced RV adverse remodelling and RA adverse remodelling, with subsequent impact on prognosis.[22 23] Differences in prognosis were, however, observed according to STR aetiology, atrial STR being characterised by significant better overall survival as compared with ventricular



Variable	AIC-value
Baseline model	3495.7

Variable	AIC-value
RVFWLS	3313.0
RVEDAi	3479.3
RASr	3484.7
RAAmaxi	3494.2

Variable	AIC-value
RVFWLS+RASr	3307.4
RVEDAi+RVFWLS	3307.6
RVFWLS+RAAmaxi	3311.9
RVEDAi+RASr	3468.7
RVEDAi+RAAmaxi	3478.8
RAAmaxi+RASr	3484.2

Variable	AIC-value
RVFWLS+RASr+RVEDAi	**3302.7**
RVEDAi+RVFWLS+RAAmaxi	3307.2
RVFWLS+RAAmaxi+RASr	3307.1
RVEDAi+RAAmaxi+RASr	3468.6

Variable	AIC-value
All variables	**3302.7**

Figure 4 Akaike information criterion (AIC) for selecting the best-fit model associated with outcome. AIC showing the different models, testing different RA/RV parameters, for selecting the best-fit model associated with outcome. The baseline model includes all variables included in the multivariable Cox regression analysis, apart from RASr, RA maximum area, RV free-wall longitudinal strain and RVEDAi. The best model is delineated in red in the figure (circle) and table (rectangle). BM, baseline model; RA, right atrium; RAAmaxi, maximal RA area—indexed for body surface area (per 5 cm^2/m^2 increase); RASr, speckle-tracking strain analysis of the RA during the reservoir-phase (per 5% increase); RV, right ventricle; RVEDAi, right ventricular end-diastolic area—indexed for body surface area (per 5 cm^2/m^2 increase); and RVFWLS, right ventricular free-wall longitudinal strain (per 5% increase).

STR, even after correcting for the important differences in clinical (including multiple comorbidities) and echocardiographic characteristics.[8]

Other previous studies have attempted to identify other prognostic factors in patients diagnosed with significant TR, including RA remodelling.[18 24 25] Recently, Hinojar *et al*[16] showed that RASr remained independently associated (HR: 0.94 (95% CI 0.89 to 0.99)) with the combined endpoint of heart failure hospitalisation and all-cause mortality in patients with severe TR at short-term follow-up (median follow-up 2.2 years), however, without adjusting for several important clinical and echocardiographic variables due to the small cohort. Moreover, using receiver operating characteristic curve analysis, a cut-off value of RASr <9.4% held the best accuracy to predict the combined endpoint (area under the receiver operating characteristic curve: 0.73, sensitivity: 73%, specificity: 65%). This value is lower as compared with the 13% cut-off (median value) used in the current manuscript. However, it was derived from a small cohort, using a different speckle-tracking software and showed poor–moderate Area Under the Curve accuracy. The current study elaborates on this concept and evaluated the association of RA size and RA function with long-term (10-year follow-up) mortality in a large cohort of patients with severe STR. Maximal RA area was associated with all-cause mortality (HR per 5 cm^2/m^2 increase: 1.144 (95% CI 1.056 to 1.239)), but only at the univariable analysis (losing statistical significance when adjusting for several relevant clinical and echocardiographic parameters). RV function (assessed by RV free-wall longitudinal strain) was also associated with all-cause mortality on univariable analysis (HR per 5% increase: 0.841 (95% CI 0.782 to 0.905)), and remained significantly associated on multivariable analysis, as previously reported.[26] Importantly, lower RA function (assessed by RASr), was not only associated with significantly worse outcomes, but maintained independent association with all-cause mortality, over several relevant covariates, including STR aetiology, RA size and RV remodelling.

Clinical implications

Current guidelines on valvular heart disease provide only limited indications for TV intervention, due to scarce and contradictory outcome data.[3 27 28] Consequently, in clinical practice, patients are often referred too late for TV intervention, due to good clinical response to diuretic therapy and referral reticence by the treating physician, knowing the high in-hospital mortality rates for isolated TV surgery (estimated around 10%).[22 23 29] Therefore, there is an unmet clinical need to optimise risk stratification in these patients and to identify low-risk patients as potential candidates for TV surgery at an earlier stage, before signs or symptoms of right heart failure occur, which will become even more important when TV percutaneous treatment will be more widely available. The current study shows, in patients with severe STR, that RA remodelling (assessed by RA size and/or RA function) precedes RV remodelling; the latter currently being used to guide the decision making in the management of severe TR.[3 27] Moreover, lower RA function was independently associated (adding incremental association value to the Cox model) with lower overall survival on top of a broad range of relevant clinical and echocardiographic variables, including RV size and RV function. Therefore, the evaluation of patients with TR should also include, in addition to the evaluation of TR severity/aetiology and RV remodelling, a comprehensive assessment of RA size and even more importantly RA function in order to optimise risk stratification and allow timely referral for TV intervention.

Study limitations

First, this study is subject to limitations of its retrospective observational design from a single tertiary centre and the results need to be confirmed and validated in larger, prospective cohorts. Second, RASr values are potentially vendor-dependent and therefore cannot be compared directly between different platforms. Third, the RASr thresholds used to define lower RA function in the current study may not be generalisable to all

patient populations. Fourth, RA assessment was performed on a dedicated RV view according to institutional protocols, which corresponded in most, yet, not all cases to the thereafter defined RV-focused apical view. Last, evaluating the RV size and RA size/function can be challenging on two-dimensional echocardiography, due to the complex geometry of these chambers. Three-dimensional echocardiography, however, was not systematically available in this patient cohort.

CONCLUSIONS

Patients diagnosed with severe STR presented with significant RA remodelling, as assessed by RA size and RA function, which precedes RV remodelling. In these patients, RASr was independently associated with overall survival and provided incremental association value over a broad range of relevant clinical and echocardiographic variables, including RA size and RV size/function.

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Patient consent for publication Not applicable.

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