Prognostic value of right atrial stiffness in systemic sclerosis

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Abstract

Objective

We hypothesised that right atrial (RA) size and mechanics may have prognostic role in systemic sclerosis (SSc) patients without manifest pulmonary arterial hypertension (PAH), thus we aimed to investigate the prognostic power of RA volume, strain and stiffness parameters alone and when added to the echocardiographic marker of RV longitudinal systolic function.

Methods

Seventy SSc patients (57±12 years) were enrolled into our follow-up study. They underwent standard echocardiographic and tissue Doppler measurements at baseline. In addition to maximal RA volume index, RA reservoir, conduit and contractile strain were measured with 2D speckle tracking technique. RA stiffness was calculated as ratio of TriE/e' to reservoir strain. Survival was assessed after 5 years. All-cause mortality was chosen as outcome. Sequential χ^2 analysis was used to evaluate the incremental prognostic benefit of adding RA volume, strain or stiffness to tricuspid S (TriS).

Results

During the follow-up period of 4.7±0.9 years, 6 patients (8.6%) died. When added to TriS in sequential Cox model, RA stiffness significantly improved the diagnostic performance of the model ($\Delta\chi2$= 3.950; p=0.047) and remained independent predictor of the outcome (HR 2.460 (1.005-6.021); p=0.049). Vmax index and strain parameters did not show incremental prognostic value over TriS. Using ROC analysis, RA stiffness ≥0.156 was the best predictor of mortality (sensitivity=83.3%, specificity =89.1%, AUC=0.859).

Conclusion

RA stiffness is associated with all-cause mortality in SSc patients without PAH independent of and incremental to the RV longitudinal systolic function. It may be proposed as non-invasive marker for identifying patients with high mortality risk.

Key words

systemic sclerosis, prognosis, right atrial function, right atrial stiffness

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease, characterised by inflammation, microvascular damage, and generalised fibrosis of the skin and various internal organs (1, 2). It has been proved that cardiac manifestation is present in a high proportion of patients and is recognised as powerful adverse prognostic factor (3, 4). Left ventricular diastolic dysfunction is associated with increased risk of mortality in SSc (5-7). Prognostic value of the subclinically impaired left ventricular systolic function has also been reported (8, 9). Predictive power of the right ventricular (RV) longitudinal systolic function is also evident in SSc (8, 9). Impaired right atrial (RA) function has also been reported in this disease, by the help of speckle tracking technique (10-12). Its prognostic value, however, remains to be seen. On the other hand, recent studies suggest, that RA size and mechanics are associated with unfavourable prognosis, not only in patients with idiopathic or connective tissue disease associated pulmonary arterial hypertension (PAH) (13, 14), but also in left heart failure, independently of the left ventricular ejection fraction (15). We thus aimed to investigate the prognostic power of the RA size and function alone and in combination with the RV longitudinal systolic function in SSc patients without manifest PAH.

Methods

Study population

Seventy consecutive patients diagnosed with SSc in the tertiary centre of the Department of Rheumatology and Immunology, Medical School, University of Pécs, Hungary, were enrolled into our follow-up study. They underwent echocardiography during a 9-month period in the year 2015. All cases complied with the updated ACR/EULAR classification criteria (16).

Patients were systematically screened for PAH. Right heart catheterisation was initiated in the presence of abnormalities suggestive of PAH (velocity of tricuspid regurgitation higher than 2.8 m/s or consistent with 2.5-2.8 m/s in the presence of unexplained dyspnoea, signs of right ventricular hypertrophy/dilatation, or a systolic D-sign; disproportional decrease of CO diffusion capacity (DLCO) compared with the forced vital capacity (FVC/DLCO >1.6), and/or DLCO<60% pred) (17). The diagnosis of PAH was based on results obtained by right heart catheterisation (mean pulmonary artery pressure ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg and pulmonary vascular resistance >3 Wood units) (18). Patients with PAH, atrial fibrillation or significant left sided valvular disease were excluded from the study. Detailed medical history was obtained.

Patients were followed for 5 years after the initial investigation with yearly scheduled visits. Patients refusing or not able to attend at the visit were consented for telephone visit for the assessment of the vital status. To avoid misclassification of the cause of death, all-cause mortality was selected as endpoint. Follow-up time was defined as the time between the date of echocardiography and the date of death or the last clinical visit.

The study complied with the Declaration of Helsinki. The institutional ethics committee approved of the study (ref.: 5338). All subjects had given written informed consent prior to inclusion.

Echocardiography

Echocardiography was performed using Philips EPIQ 7G ultrasound system (Philips Healthcare, Best, The Netherlands) by a single investigator. Left ventricular ejection fraction was measured by biplane Simpson's method. Basal, mid-cavity, and longitudinal dimensions of the RV were obtained at end-diastole in RV–focused apical 4-chamber view and corrected for body surface area (BSA). Tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (RVFAC) were measured, as parameters of the RV systolic function. Maximal and minimal diameters of the inferior vena cava were measured in subxiphoid view. Collapsibility index (the percent decrease in the diameter of inferior vena cava with inspiration) was calculated. RV wall thickness was obtained from subxiphoid view by 2D echocardiography at end-diastole. Se-

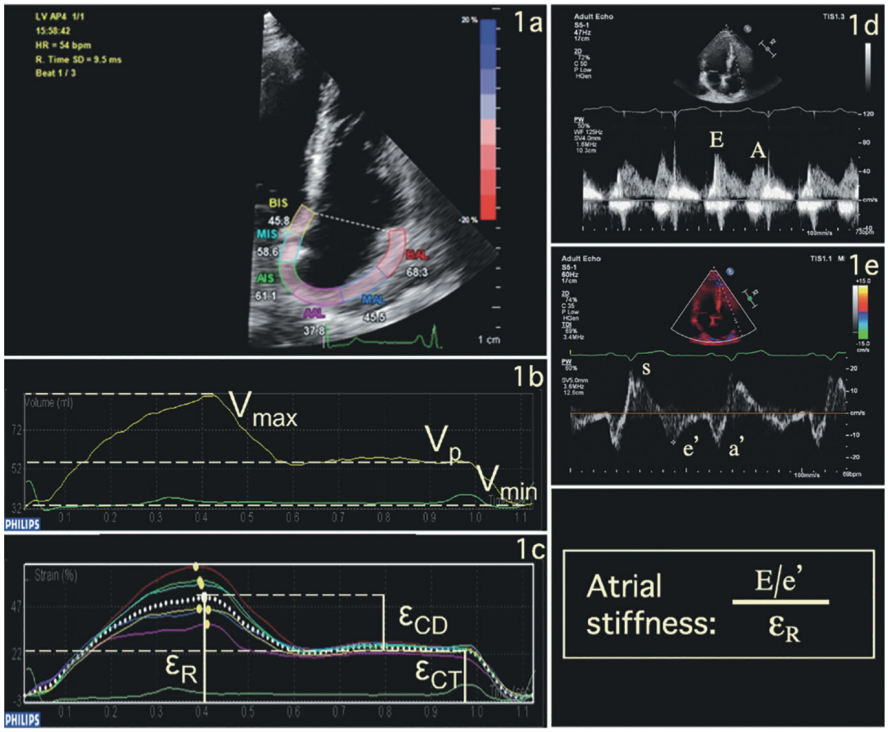


Fig. 1. RV-focused apical 4-chamber view depicting the region of interest **(1a)** and the RA strain curve created by the speckle-tracking software **(1c)**. Using the atrial borders created for speckle-tracking analysis, RA volume curves were generated by the same software **(1b)**. Spectral Doppler curve of the transtricuspid flow **(1d).** Pulsed tissue Doppler curve measured on the lateral border of the tricuspid annulus **(1e)**.
ε_R: RA reservoir strain; ε_{CD}: RA conduit strain; ε_{CT}: RA contractile strain; Vmax: maximal RA volume; Vmin: minimal RA volume; Vp: volume at the beginning of P-wave; E: early-diastolic wave of the tricuspid inflow; A: late-diastolic wave of the tricuspid inflow; systolic (S), early-(e') and late-(a') diastolic myocardial velocities.

verity of tricuspid regurgitation was assessed according to the current recommendations and classified as mild, moderate, or severe. Systolic pulmonary artery pressure was estimated as a sum of the pressure difference across the tricuspid valve (calculated using the modified Bernoulli equation) and an estimate of mean RA pressure (5 to 15 mmHg) using the diameter and collapsibility index of the inferior vena cava (19). In addition to the spectral Doppler parameters of the transmitral and transtricuspid flow (E, A) (Fig. 1d), myocardial systolic (S), early (e') and late (a') diastolic velocities were measured in apical 4-chamber view at the septal and lateral border of the mitral annulus as well as on the lateral border of the tricuspid annulus (Fig. 1e) using pulsed tissue Doppler imaging. Mitral and tricuspid E/A and E/e' ratios were calculated. Doppler measurements were obtained from ≥3 consecutive beats during end-expiratory apnoea. Left ventricular diastolic function was evaluated in accordance with the current recommendation (20). Impaired RV longitudinal systolic function was defined as TriS<10 cm/s (19). Elevated RV filling pressure was diagnosed if TriE/e'> 6 (19).

Right atrial strain and volume measurements

For atrial speckle tracking analysis, RV-focused apical 4-chamber view movies were obtained using 2D echocardiography. Care was taken to obtain true apical images to avoid foreshortening. Image contrast, depth and sector size were adjusted to achieve adequate frame rate (80 and 90 frames/s) and optimise RA border visualisation. Three consecutive heart cycles were recorded digitally. Recordings were processed by a single investigator blinded to standard echocardiographic and clinical data of the patients, using a dedicated software (QLab 10.5, Philips Healthcare, Andover, MA, USA), allowing off-line semi-automated analysis of speckle tracking-based strain (Fig. 1a). The beginning of the QRS was predefined by the software as reference point. The first positive peak of the curve was measured at the end of the reservoir phase, just before tricuspid valve opening (RA reservoir strain). This was followed by a plateau and a second late peak at the peak of the P wave on the electrocardiogram (RA contractile strain). RA conduit strain was defined as the difference between reservoir and contractile strain (21) (Fig. 1c). RA stiffness was calculated as ratio of TriE/e' to RA reservoir strain (22-24).

Using the atrial borders created for speckle tracking analysis, RA volume curves were generated by the same software (Fig. 1b). Volume calculation was based on Simpson's single plane method of disks. Maximal RA volume was measured at the end of T wave on electrocardiogram, just before the opening of the tricuspid valve, and indexed for BSA (RA Vmax index).

Statistical analysis

Categorical data were expressed as frequencies and percentages; continuous data were expressed as the mean ± SD. Comparisons of data between two groups were performed using independent-sample t-tests or Mann-Whitney test for continuous variables and χ^2 tests for categorical variables.

Univariable and multiple Cox proportional-hazards models were applied. Hazard ratios (HR) were calculated with 95% confidence intervals (CI). Models were set up based on variables with $p<0.1$ in univariable analysis. Sequential χ^2 analysis was used to evaluate the incremental prognostic benefit of adding RA volume, strain or stiffness to TriS. C-statistics were applied to compare multivariable Cox models, with values greater than 0.7 representing acceptable models. In order to input them into Cox models, RA stiffness and NT-proBNP data were standardised by calculating a z-score for each value.

Receiver-operating characteristic (ROC) curves were used to examine the diagnostic performance of RA stiffness in predicting all-cause mortality. Area un-

Table I. Clinical characteristics of the entire study population at baseline and data stratified by RA stiffness values.

Variable	All patients (n=70)	RA stiffness <0.156 (n=58)	RA stiffness ≥0.156 (n=12)	*p*
Age (years)	57 ± 12	56 ± 12	64 ± 7	**0.030**
Body surface area (m^2)	1.75 ± 0.19	1.76 ± 0.20	1.74 ± 0.14	0.781
Female gender n (%)	63 (90)	52 (90)	11 (92)	0.833
Disease duration (years)	7.2 ± 5.8	6.8 ± 5.0	8.8 ± 8.7	0.456
Limited cutaneous form n (%)	32 (46)	27 (46.5)	5 (42)	0.757
Modified Rodnan skin score	11.3 ± 8.0	10.8 ± 7.5	14.3 ± 10.1	0.187
Follow-up time (days)	1721 ± 344	1768 ± 234	1491 ± 623	0.155
Death n (%)	6 (9)	1 (2)	5 (42)	**<0.001**
Anti-Centromere Antibody n (%)	18 (26)	14 (24)	4 (33)	0.577
Anti-Topoisomerase I Antibody n (%)	20 (29)	14 (24)	6 (50)	**0.042**
Coronary artery disease n (%)	2 (3)	1 (2)	1 (8.5)	0.211
Systemic arterial hypertension n (%)	36 (51)	30 (52)	6 (50)	0.913
Angiotensin convertase enzyme inhibitors n (%)	33 (47)	29 (50)	4 (33)	0.378
Calcium channel blockers n (%)	36 (51)	28 (48)	8 (67)	0.246
Loop diuretics n (%)	31 (44)	24 (41)	7 (58)	0.282
Mineralocorticoid receptor antagonists n (%)	18 (26)	14 (24)	4 (33)	0.507
New York Heart Association I	20 (28)	19 (33)	1 (8.5)	**0.014**
functional class n (%) II	32 (46)	28 (48)	4 (33)	
III	18 (26)	11 (19)	7 (58.5)	
6-minute walking distance (m)	391 ± 95	405 ± 95	323 ± 61	**0.006**
Modified Borg dyspnoea index	1.7 ± 1.6	1.6 ± 1.6	2.1 ± 1.8	0.286
Erythrocyte sedimentation rate (mm/h)	21.9 ± 16.0	20.9 ± 15.8	26.6 ± 17.3	0.269
C-reactive protein (mg/l)	3.6 ± 5.5	3.3 ± 5.4	4.9 ± 5.9	0.357
Creatinine (μmol/l)	70.6 ± 23.7	70.8 ± 24.7	70.0 ± 18.4	0.919
NT-proBNP (pg/ml)	192.0 ± 163.0	164.4 ± 136.4	325.6 ± 217.6	**0.007**
Troponin-T (ng/l)	12.0 ± 11.2	9.3 ± 7.9	19.5 ± 15.6	0.090
Forced vital capacity (%)	100.5 ± 15.0	101.4 ± 15.4	96.1 ± 12.4	0.265
Diffusing capacity of carbon monoxide (%)	64.5 ± 15.1	67.2 ± 13.9	51.4 ± 14.8	**0.001**

Statistically significant *p*-values ($p<0.05$) are given in bold.

der the curve (AUC) value was calculated. Optimal cut-off value was chosen to maximise sensitivity and specificity. Based on this cut-off value, Kaplan-Meier survival curve was created and differences between groups were tested by Mantel-Cox log rank test.

Prognostic power of concordant *versus* discordant values for TriS and RA stiffness were also evaluated: three groups were created defined by dividing each variable at the cut-off value (high TriS AND low RA stiffness; low TriS OR high RA stiffness; low TriS AND high RA stiffness). Kaplan-Meier survival curve was created and differences between groups were tested by Mantel-Cox log rank test.

To determine intraobserver variability, assessment of RA strain and volume parameters was repeated 2 and 4 weeks after the index measurements in 30 randomly selected patients by the same investigator. To calculate interobserver variability, assessment of RA strain and volume parameters was repeated by another experienced cardiologist in 20 randomly selected patients. Intraobserver and interobserver variability was assessed by the intraclass correlation coefficient.

A *p*-value of <0.05 was considered significant. The data were analysed using IBM SPSS 27 statistical software.

Results

Clinical and echocardiographic characteristics

Seventy SSc patients were enrolled into the study. At baseline, mean age of the study cohort was 57±12 years. 32 (46%) patients had limited cutaneous while 38 (54%) patients had diffuse cutaneous form of the disease. Table I and Table II summarise the clinical and echocardiographic characteristics of the population. Comparison of the echocardiographic data with an age and gender matched healthy population has already been reported (12).

Left ventricular ejection fraction was preserved (≥55%) in 68 (97%) and mildly reduced (45–54%) in 2 (3%) patients. Left ventricular diastolic function was preserved in 20 (28.6%) patients whereas elevated left ventricular filling pressure was found in 15 (21.4%) patients. RV dimensions, RV wall thickness and pulmonary artery pressure values were within the normal range. TriS <10 cm/s were found in 8 (11.4%) patients. TriE/e' suggested elevated RV filling pressure in 22 (31.4%) patients.

Intra- and interobserver variability

Intraclass correlation coefficients for intraobserver variability were 0.91, 0.96, 0.91 and 0.93 for reservoir, contractile and conduit strain and for Vmax, respectively. Regarding interobserver variability, intraclass correlation coefficients for reservoir, contractile and conduit strain and for Vmax were 0.89, 0.88, 0.87 and 0.91, respectively.

Associations of outcome

During the follow-up period of 4.7±0.9 years, 6 patients (8.6%) died. No patient was lost to follow-up.

Among all clinical and laboratory parameters, known coronary artery disease, NT-proBNP, and troponin-T levels showed significant correlation with the outcome whereas 6-minute walking distance and diffusing capacity of carbon monoxide (DLCO) showed borderline significance. Left ventricular ejection fraction not, but the grade of left ventricular diastolic dysfunction showed significant association with all-cause mortality in univariate Cox regression analyses.

In addition to the systolic pulmonary artery pressure, parameters of the RV longitudinal systolic function (TAPSE and TriS) and RV filling pressure (TriE/e') became significant predictors of mortality. RA Vmax index showed significant association with outcome, whereas reservoir and conduit strain parameters of the RA function did not. Regarding contractile strain, the association showed borderline significance. RA stiffness, in contrast, became significant predictor of mortality in univariate analysis. Results of the univariate Cox regression analyses are reported in Table III.

Table II. Echocardiographic characteristics of the entire study population at baseline and data stratified by RA stiffness values.

Variable		All patients (n=70)	RA stiffness <0.156 (n=58)	RA stiffness ≥0.156 (n=12)	*p*
Left ventricular ejection fraction (%)		60.8 ± 4.5	60.7 ± 4.7	60.8 ± 3.8	0.949
Left ventricular diastolic function n (%)	Normal	20 (28.6)	20 (34.5)	0	0.052
	Impaired relaxation	35 (50)	27 (46.5)	8 (66.6)	
	Pseudonormal	15 (21.4)	11 (19)	4 (33.3)	
Grade of tricuspid regurgitation n (%)	Mild	63 (90)	53 (91)	10 (84)	0.445
	Moderate	5 (7)	4 (7)	1 (8)	
	Severe	2 (3)	1 (2)	1 (8)	
Pulmonary arterial systolic pressure (mm Hg)		26.2 ± 5.7	25.1 ± 5.0	30.2 ± 6.8	**0.008**
RV basal diameter index (mm/m^2)		18.4 ± 2.4	18.3 ± 2.6	19.1 ± 1.5	0.287
RV mid-cavity diameter index (mm/m^2)		13.5 ± 2.1	13.4 ± 2.2	13.9 ± 1.4	0.512
RV longitudinal diameter index (mm/m^2)		31.7 ± 3.6	31.8 ± 3.7	31.2 ± 3.2	0.606
Inferior vena cava (mm)		14.0 ± 3.8	14.3 ± 3.5	12.3 ± 4.7	0.119
Collapsibility index (%)		55.5 ± 11.5	55.6 ± 11.8	55.9 ± 9.6	0.910
RV wall thickness (mm)		5.0 ± 1.0	5.0 ± 1.0	5.0 ± 1.1	0.894
RVFAC (%)		47.5 ± 7.2	47.9 ± 6.0	46.0 ± 11.4	0.426
TAPSE (mm)		21.1 ± 2.6	21.6 ± 2.3	18.8 ± 3.0	**0.001**
Tricuspid E (cm/s)		47.5 ± 9.2	46.7 ± 9.7	51.4 ± 5.2	0.101
Tricuspid A (cm/s)		39.5 ± 8.8	38.0 ± 8.0	46.6 ± 9.2	**0.002**
Tricuspid e' (cm/s)		9.5 ± 2.3	10.1 ± 2.4	6.9 ± 1.2	**<0.001**
Tricuspid a' (cm/s)		13.2 ± 2.6	13.5 ± 2.5	12.0 ± 2.4	0.074
Tricuspid S (cm/s)		12.4 ± 2.3	12.8 ± 2.1	10.4 ± 2.2	**0.001**
Tricuspid E/e'		5.3 ± 1.5	4.8 ± 1.1	7.6 ± 1.2	**<0.001**
RA size and function					
RA Vmax index (mL/m^2)		19.4 ± 5.5	18.8 ± 4.8	22.6 ± 7.8	0.171
RA reservoir strain (%)		49.3 ± 10.7	50.5 ± 10.2	43.6 ± 11.4	**0.041**
RA contractile strain (%)		22.9 ± 5.8	23.0 ± 5.1	22.5 ± 8.4	0.770
RA conduit strain (%)		26.8 ± 8.1	27.6 ± 7.5	22.9 ± 10.0	0.066
RA stiffness		0.112 ± 0.039	0.098 ± 0.024	0.180 ± 0.021	**<0.001**

When added to TriS in sequential Cox model, RA stiffness significantly improved the diagnostic performance of the model ($\Delta\chi^2$= 3.950; p=0.047) and remained independent predictor of the outcome (HR 2.460 (1.005-6.021); p=0.049). In contrast, Vmax index and RA contractile strain did not show incremental prognostic value over TriS in the χ^2 model (Table IV).

Discriminative ability of RA stiffness

To demonstrate the performance of RA stiffness in predicting all-cause mortality, ROC curve was created, with an AUC of 0.859. The optimal cut-off point for predicting all-cause mortality was 0.156. Patients with RA stiffness equal or above this cut-off value had significantly higher risk for death (log-rank p<0.001). ROC curve and Kaplan-Meier cumulative survival curve demonstrating the predictive power of the RA stiffness are presented in Figure 2.

Clinical and echocardiographic characteristics of the study cohort stratified by the cut-off RA stiffness value are shown in Table I and Table II. Patients with elevated RA stiffness were significantly older and their walking distance was significantly shorter compared with the other subgroup. Significantly higher NT-proBNP levels whereas significantly lower DLCO values were found in these patients. Anti-topoisomerase I antibody positivity was also more common in this subgroup.

Left ventricular ejection fraction values were similar in the two subgroups. Patients with high RA stiffness exhibited worse left ventricular diastolic function, though this difference has borderline significance. Global RV systolic function (RVFAC) was preserved in both subgroups. Parameters reflecting the RV longitudinal systolic function (TAPSE, TriS), however, were significantly lower in patients with RA stiffness above the cut-off. Significantly lower Trie' and higher TriE/e' values were also found in these patients. Systolic pulmonary artery pressure was significantly higher in this subgroup, but still within the normal range.

Incremental prognostic value of RA stiffness

When evaluated by comparing groups above and below the cut-off value (10 cm/s for TriS and 0.156 for RA stiffness) for each parameter, patients with high TriS AND low RA stiffness (n=55) showed the lowest mortality rate (1 event (1.8%)). Compared with this reference group, patients with low TriS OR high RA stiffness (n=10) had significantly higher mortality rate (2 events (20%); log-rank p=0.008) whereas the highest mortality rate was observed in patients with low TriS AND elevated RA stiffness (n=5, 3 events (60%), log-rank p<0.001) (Fig. 3).

Discussion

SSc is a connective tissue disease characterised by vascular abnormalities and diffuse fibrosis of the skin and various internal organs (1, 2). Cardiac involvement implies poor prognosis in SSc (3, 4), thus its early recognition would be crucial, with non-invasive tools allowing pre-clinical identification of the damages. Novel echocardiographic techniques, such as tissue Doppler imaging or speckle tracking based strain measurements may provide useful information about the early myocardial involvement in this disease.

Myocardial fibrosis may lead to left ventricular diastolic dysfunction, which is highly prevalent in SSc and is associated with increased risk of mortality (5-7). Prognostic value of the increased left atrial volume was also reported (6). Myocardial fibrosis may also eventuate in subclinically impaired left ventricular systolic function (9, 25, 26). Both speckle tracking-derived left ventricular global longitudinal (9) and circumferential strain (8) showed significant associations with the outcome in this condition. Nevertheless, in SSc myocardial mechanics is impaired not only in the left, but also in the right heart (27). Both TriS (8) and TAPSE (9) showed significant, independent association with the adverse outcome.

After decades of focusing on ventricular function, nowadays more attention

Table III. Univariate Cox regression analysis of associations with all-cause mortality in patients with SSc.

Variable	HR (95% CI)	*p*
Clinical characteristics		
Age (years)	1.029 (0.951-1.113)	0.472
Body surface area (m^2)	0.278 (0.003-28.131)	0.587
Female gender	0.502 (0.059-4.298)	0.529
Disease duration (years)	1.049 (0.935-1.177)	0.415
Limited cutaneous form	0.350 (0.063-1.940)	0.229
Modified Rodnan skin score	1.047 (0.957-1.146)	0.314
Anti-Centromere Antibody positivity	1.490 (0.273-8.140)	0.645
Anti-Topoisomerase I Antibody positivity	2.136 (0.427-10.676)	0.355
Coronary artery disease	10.170 (1.171-88.354)	**0.035**
Systemic arterial hypertension	1.082 (0.215-5.442	0.923
Angiotensin convertase enzyme inhibitor use	0.844 (0.169-4.216)	0.837
Calcium channel blocker use	5.244 (0.612-44.952)	0.131
Loop diuretics use	1.469 (0.269-8.024)	0.657
Mineralocorticoid receptor antagonist use	2.939 (0.593-14.569)	0.187
New York Heart Association functional class	2.380 (0.714-7.938)	0.158
6-minute walking distance (m)	0.993 (0.985-1.001)	*0.079*
Modified Borg dyspnoea index	1.171 (0.763-1.798)	0.469
Erythrocyte sedimentation rate (mm/h)	0.996 (0.945-1.050)	0.885
C-reactive protein (mg/l)	0.979 (0.824-1.163)	0.809
Creatinine (μmol/l)	0.999 (0.963-1.037)	0.969
NT-proBNP (pg/ml)	2.447 (1.299-4.609)	**0.006**
Troponin-T (ng/l)	1.070 (1.024-1.118)	**0.003**
Forced vital capacity (%)	0.972 (0.911-1.036)	0.382
Diffusing capacity of carbon monoxide (%)	0.956 (0.912-1.002)	*0.061*
Echocardiographic characteristics		
Left ventricular ejection fraction (%)	1.007 (0.840-1.206)	0.942
Grade of left ventricular diastolic dysfunction	6.751 (1.428-31.909)	**0.016**
Grade of tricuspid regurgitation	3.113 (1.330-7.283)	**0.009**
Pulmonary arterial systolic pressure (mm Hg)	1.130 (1.003-1.272)	**0.044**
RV basal diameter index (mm/m^2)	1.167 (0.862-1.579)	0.318
RV mid-cavity diameter index (mm/m^2)	1.154 (0.792-1.682)	0.455
RV longitudinal diameter index (mm/m^2)	1.111 (0.897-1.376)	0.334
Inferior vena cava (mm)	1.026 (0.812-1.295)	0.832
Collapsibility index (%)	1.053 (0.961-1.153)	0.272
RV wall thickness (mm)	0.953 (0.436-2.080)	0.903
RVFAC (%)	0.976 (0.867-1.099)	0.689
TAPSE (mm)	0.638 (0.445-0.914)	**0.014**
Tricuspid E (cm/s)	1.039 (0.969-1.114)	0.282
Tricuspid A (cm/s)	1.049 0.976-1.127)	0.192
Tricuspid e' (cm/s)	0.735 (0.492-1.100)	0.134
Tricuspid a' (cm/s)	0.676 (0.439-1.043	*0.077*
Tricuspid S (cm/s)	0.548 (0.355-0.848)	**0.007**
Tricuspid E/e'	2.002 (1.220-3.285)	**0.006**
RA size and function		
RA Vmax index (mL/m^2)	1.202 (1.061-1.362)	**0.004**
RA reservoir strain (%)	0.952 (0.874-1.036)	0.253
RA contractile strain (%)	0.839 (0.690-1.020)	*0.079*
RA conduit strain (%)	0.978 (0.877-1.091)	0.690
RA stiffness	3.185 (1.544-6.570)	**0.002**

Statistically significant *p*-values ($p<0.05$) are given in bold. $0.05 \leq p < 0.1$ values are given in italics.

is given to the atrial size and mechanics. Lindqvist *et al*. found enlarged RA area in SSc patients without manifest PAH (28). Similarly, D'Andrea *et al*. reported significant enlargement of the RA area compared with healthy subjects (11), while Durmus *et al*. found RA area index values similar to those in healthy persons (10). Significantly decreased RA segmental strain values were reported by D'Andrea *et al*. in SSc patients, especially in those with pulmonary fibrosis (11). Durmus *et al*. found decreased reservoir and conduit strain values compared to a healthy control population (10). The previous findings of our group were in line with the results of Durmus *et al*.: RA volume values were similar in SSc patients without manifest PAH and in the control group, but significantly decreased reservoir and conduit strain values were found in the SSc group. Contractile strain values did not differ between SSc group and healthy persons (12). Despite these data, the prognostic value of RA size and mechanics has never been investigated in SSc.

Recent studies suggested, however, that RA size and mechanics are associated with unfavourable prognosis in patients with idiopathic or connective tissue disease associated PAH (13, 14). In addition, Jain *et al*. proved, that RA reservoir and conduit strain are independent predictors of mortality in left heart failure with both preserved and reduced ejection fraction (15).

Thus, we hypothesised that RA size and mechanics may have prognostic role even in SSc patients without manifest PAH and aimed to investigate the prognostic power of the RA volume, strain and stiffness parameters alone and when added to the echocardiographic marker of the RV longitudinal systolic function.

In univariate Cox regression analysis RA Vmax index and RA stiffness showed significant association with 5-year all-cause mortality, whereas RA contractile strain showed borderline significance with the outcome. When added to TriS in sequential Cox model, RA stiffness significantly improved the diagnostic performance of the model and remained independent predictor of the outcome. Our data support the strong prognostic value of RA stiffness in SSc patients without manifest PAH. RA stiffness is a complex parameter reflecting atrial mechanics and RV filling pressure simultaneously. This may explain its superiority over the RA volume and strain parameters.

Atrial stiffness is a novel echocardiographic parameter of the atrial performance. It represents the change in pressure required to increase the volume of the atrium in a given measure (22, 23). The diagnostic role of this parameter was first described in the left heart: Kurt *et al*. reported left atrial stiffness as an accurate index to distinguish diastolic heart failure patients from those with

Table IV. Models of sequential Cox regression analysis for predicting outcome in SSc.

		Model 1	Model 2	Model 3
C-statistics	0.721	0.737	0.820	0.849
$\Delta\chi^2$		2.376; p=0.123	2.536; p=0.111	3.950; ***p*=0.047**
Variables in model	**HR (95%CI) *p*-value**	**HR (95%CI) *p*-value**	**HR (95%CI) *p*-value**	**HR (95%CI) *p*-value**
Tricuspid S (cm/s)	0.548 (0.355-0.848); ***p*=0.007**	0.687 (0.421-1.122); p=0.134	0.599 (0.399-0.901); ***p*=0.014**	0.768 (0.464-1.271); p=0.304
RA Vmax index (ml/m^2)		1.114 (0.967-1.283); p=0.135		
RA contractile strain (%)			0.867 (0.716-1.049); p=0.141	
RA stiffness				2.460 (1.005-6.021); ***p*=0.049**

C-statistics represents the overall performance of the predictive model. $\Delta\chi^2$ reflects the incremental prognostic value of the RA variables over TriS, when added to the model. Statistically significant p-values (p<0.05) are given in bold.

asymptomatic diastolic dysfunction (22). In the study of Porpáczy *et al*. left atrial stiffness was superior to left atrial Vmax index and reservoir strain in predicting elevated NT-proBNP levels in SSc patients (29). In the right heart, Teixeira et al. demonstrated increased RA stiffness in patients with left heart failure (24). Besides, in our previous study, RA stiffness was proved to be significantly elevated in SSc patients, compared with healthy subjects, and showed significant correlation with the functional capacity of the patients (12). In the study of Pilichowska-Paszkiet *et al*. fibrosis of the left atrial wall was detected by electroanatomical mapping. Left atrial stiffness showed robust correlation with the extent of this fibrosis in patients with atrial fibrillation (30). Similar histopathologic evidence is not available in the right heart. Still, elevated RA stiffness may represent the extent of the replacement fibrosis affecting the RA wall, as it was reported in the left heart (31).

In SSc, impairment of the RV function and the subsequent RA dysfunction and dilatation are traditionally attributed to the development of PAH or PH due to severe pulmonary fibrosis (32). Similar findings, however, has been proved in SSc patients even without the resting elevation of the pulmonary pressure (8-10, 12, 27, 28). In SSc patients without resting PAH, RV myocardial dysfunction may be considered as the sign of the primary myocardial involvement of the disease (27). On the other hand, in SSc patients with interstitial lung disease or subclinical pulmonary vascular disease, the subclinical elevation of the pulmonary vascular resistance may be unmasked by exercise, when pulmonary circulation no longer has the capacity to adapt, and the pulmonary pressure increases parallel with the increasing cardiac output (33). This exercise-induced, intermittent pressure overload may also lead to ultrastructural changes in the right heart (27, 28). In addition, independently from the aetiology, left ventricular diastolic dysfunction is often associated with impaired mechanics of the right heart. This phenomenon is thought to be explained by the exercise-induced elevation of left ventricular filling pressure and the con-

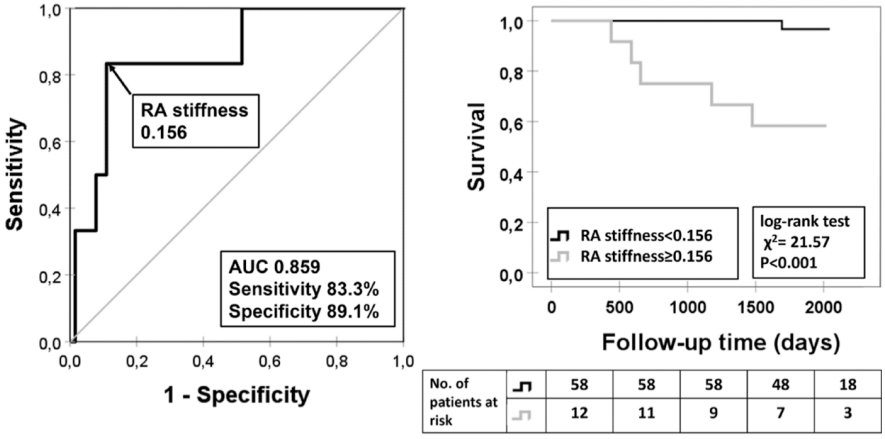
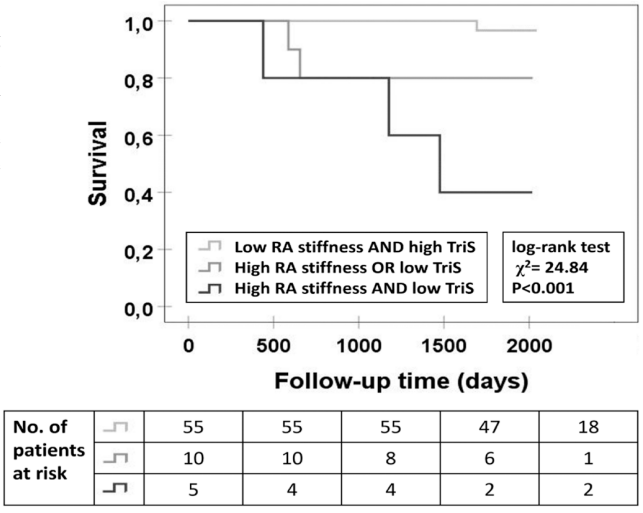


Fig. 2. ROC curve and Kaplan-Meier survival curve demonstrating the performance of RA stiffness in predicting all-cause mortality.

Fig. 3. Kaplan-Meier survival curve demonstrating the incremental prognostic value of RA stiffness when added to TriS in predicting all-cause mortality. The cohort was stratified by the TriS and RA stiffness profile of the patients.



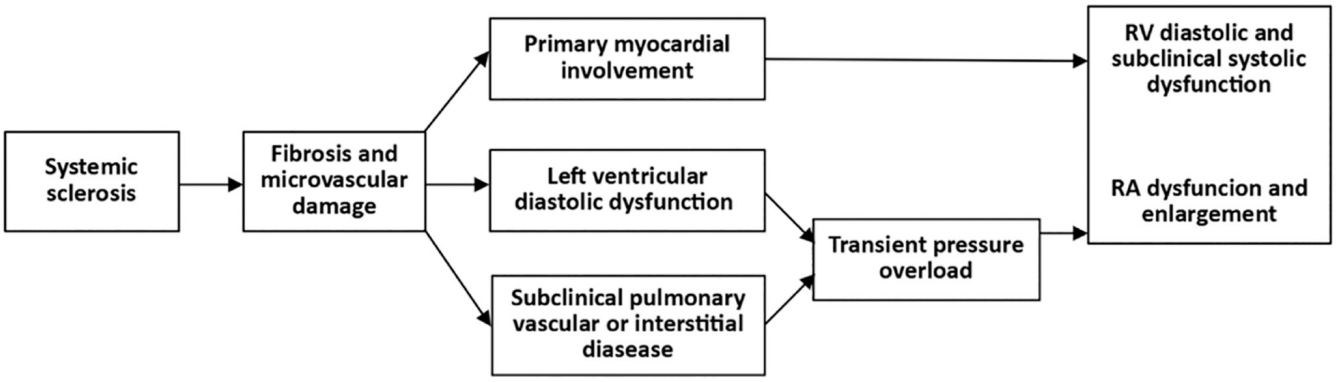


Fig. 4. Mechanisms involved in the development of RA dysfunction and enlargement in SSc patients without manifest PAH.

sequential elevation of the pulmonary artery pressure (34) (Fig. 4).

When stratified by RA stiffness cut-off, our data may support all these hypotheses: high risk patient with RA stiffness above the cut-off exhibited significantly higher pulmonary arterial systolic pressure (but still within the normal range) and significantly lower DLCO values. Besides, there was a clear tendency suggesting worse left ventricular diastolic function in the high-risk subgroup, though the difference was not statistically significant. Diagnostic and prognostic utility of the well know cardiac biomarkers, NT-proBNP and troponin-T has already been proved in SSc (35-37). Patient with RA stiffness above the cut-off showed significantly higher NT-proBNP values. Troponin-T level was also higher in this subgroup, albeit the differences were not statistically significant. Anti-topoisomerase I antibody positivity was also significantly more common in the high-risk subgroup. The potential clinical significance of this antibody level has been reported in evaluating disease severity and prognosis in SSc (38, 39).

Limitations of the study

Our data should be interpreted in the context of their limitations. First, the statistical power of our analysis is limited by the relatively low number of participants and events. Our results require further validation in a larger SSc population. For obtaining RA strain values, we used a software that was developed for left ventricular strain analysis because a dedicated software for atrial strain estimation was not available. RV strain may better reflect the subclinical impairment of the RV systolic function than our traditional and tissue Doppler parameters. Nevertheless, in the lack of appropriate analytical software, RV strain analysis was not performed in our study.

Conclusion

RA stiffness is associated with all-cause mortality in SSc patients without PAH independent of and incremental to the RV longitudinal systolic function. It may be proposed as a non-invasive marker for identifying SSc patients with high mortality risk.

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