LEFT ATRIAL MECHANICS IN SYSTEMIC SCLEROSIS

PhD thesis

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1. INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by inflammation and fibrosis in various organs. Cardiac manifestations of the disease are common but often clinically asymptomatic and may represent a diagnostic challenge: Left ventricular (LV) systolic dysfunction is rare in SSc, but diastolic dysfunction and the consequential heart failure with preserved ejection fraction (HFpEF) are much more frequent. They reflect the primary myocardial involvement of the disease. Many symptoms characteristic of SSc (dyspnea, leg oedema, exercise intolerance) are associated with LV diastolic dysfunction and elevated LV filling pressure. These typical symptoms of heart failure (HF), however, are often mistaken for pulmonary arterial hypertension (PAH) or interstitial lung disease, thus, HFpEF is significantly underdiagnosed in these patients. Therefore, early and reliable detection of LV diastolic dysfunction and elevated filling pressure has important diagnostic and prognostic implications in SSc. In the everyday practice, echocardiography is used for this purpose. Although multiple echocardiographic indices have been applied for the diagnosis, including E/A ratio, e' velocity, E/e' ratio, left atrial (LA) volume, LV hypertrophy and tricuspid regurgitation velocity, current echocardiographic criteria lack sensitivity. It is evident, that additional echocardiographic parameters are required. Recent studies have proved, that parameters of the LA function showed good correlation with the degree of diastolic dysfunction and LV filling pressure, exceeding the diagnostic power of the conventional echocardiographic parameters. Nowadays therefore, more and more attention has been focused on the analysis of the LA mechanics.

LA function may be obtained by 2-dimensional (2D) echocardiography, based on volumetric measurements. On the other hand, increasing evidence suggests that 2D speckle tracking–derived strain imaging (STE) is a highly promising and feasible technique for this purpose. LA stiffness is a further parameter of the atrial performance, representing the change in pressure required to increase the volume of the atrium in a given measure.

In SSc few data are available about LA size and function and little is known about the importance of LA mechanics in this disease.

2. OBJECTIVES

The aim of the present work was to investigate the correlation between LV diastolic function and LA mechanics in SSc patients with the use of volumetric and 2D STE-derived strain techniques and to compare the results with those obtained in healthy subjects.

In addition, we aimed to compare the diagnostic power of LA volumetric and functional parameters (V_{max} index, reservoir strain (ε_R) and stiffness) in predicting elevated LV filling pressure in SSc patients. N-terminal pro-B-type natriuretic peptide (NT-proBNP) served as non-invasive measure of the LV filling pressure in this study.

3. METHODS

3.1. Study population

Eighty consecutive patients diagnosed with SSc, were recruited for this prospective study. Patients with PAH, atrial fibrillation, significant left-sided valvular disease, or known coronary artery disease were excluded from the study. Data from the investigation of an age and sex-matched group of 30 healthy volunteers without the signs or symptoms of any cardiac disease were used as control.

3.2. Echocardiography

Measurement of the conventional echocardiographic parameters was carried out according to the current recommendations. Based on LV diastolic function SSc patients were subgrouped according to the following categories:

I: normal (lateral e' ≥ 10 cm/s, septal e' ≥ 7 cm/s, E/A ≥ 0.8, E/e' < 10)

II: impaired relaxation (lateral e' < 10 cm/s, septal e' < 7 cm/s, E/A < 0.8, E/e' < 10)

III: pseudonormal physiology (lateral e' < 10 cm/s, septal e' < 7 cm/s, E/A 0.8–2, E/e' 10 –14)

IV: restrictive physiology (lateral e' < 10 cm/s, septal e' < 7 cm/s, E/A >2, E/e' > 14)

3.3. Strain measurements

For atrial speckle tracking analysis, apical four- and two-chamber view movies were obtained by means of 2D echocardiography. The frame rate was set at 80–90 frames/sec. Recordings were processed offline with the use of dedicated software (QLab; Philips Healthcare, Andover, MA, USA), by a single investigator, blinded to the clinical, laboratory and conventional echocardiographic data. The first positive peak of the curve was measured at the end of the

reservoir phase, just before mitral valve opening (reservoir strain, ε_R). This was followed by a plateau and a second late peak at the onset of the P-wave on the electrocardiogram (contractile strain, ε_{CT}). The conduit strain (ε_{CD}) was defined as the difference between the reservoir and the contractile strain.

LA stiffness was calculated as ratio of E/e′ to LA reservoir strain.

With the use of the same software, LV global longitudinal strain (GLS) also was estimated.

3.4. Volumetric parameters of the left atrium

LA volume curves were generated by the same software using the endocardial borders created for speckle tracking analysis, in the apical four- and two-chamber views both. LA volumes were measured at different time points of the cardiac cycle: maximal LA volume (V_{max}) at the end of the T-wave on the electrocardiogram, just before the mitral valve opening; minimal LA volume (V_{min}) at the QRS complex, just after the mitral valve closure; and volume at atrial contraction (V_p) at the beginning of P-wave. Values from the two views were averaged and indexed for BSA (V_{max}-, V_{min}- and V_p index). The following phasic volume indices of the LA function were calculated:

Total emptying fraction (TEF): $([V_{max} - V_{min}]/V_{max}) \times 100$

Expansion index (EI): $([V_{max} - V_{min}]/V_{min}) \times 100$

Active emptying fraction (AEF): $([V_p - V_{min}]/V_p) \times 100$

Passive emptying fraction (PEF): $([V_{max} - V_p]/V_{max}) \times 100$

TEF and EI have been assumed to reflect LA reservoir function and AEF and PEF to reflect LA contractile and conduit function, respectively.

3.5. NT-proBNP measurements

Blood samples were obtained immediately prior to the echocardiographic studies. Plasma concentrations of NT-proBNP were analysed by electrochemiluminescence immunoassay. NT-proBNP value > 220 pg/ml was defined as the evidence of the elevated LV filling pressure.

3.6. Statistical analysis

Comparisons of data between two groups were performed using independent-sample t-tests or independent Mann–Whitney test and chi square. Comparisons of data between more groups were performed with the use of multivariate analysis of variance (MANOVA) with Tukey post hoc test. Relationship between lnNT-proBNP and the investigated echocardiographic parameters was assessed using linear regression analysis. Potential determinants of the NT-

proBNP level (age, BSA, estimated glomerular filtration rate (eGFR), LV EF, and duration of the disease) were also included into the analysis. In the second step, multiple stepwise linear regression analysis was performed, by entering those variables with $p < 0.1$ in the univariate analysis. Variance Inflation Factor (VIF) values above 2.5 were considered to have potential multicollinearity. Receiver-operating characteristic (ROC) curves were used to examine the diagnostic performance of the echocardiographic parameters in predicting elevated LV filling pressure. Area under the curve (AUC) values were calculated. To determine intraobserver variability, assessment of LA 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 LA strain and volume parameters was repeated by another experienced cardiologist in 20 randomly selected patients. A p value of < 0.05 was considered significant.

4. RESULTS

From the total cohort of 80 patients, 72 were eligible for the study. Intraclass correlation coefficients (ICC) for intraobserver variability were 0.982, 0.945, 0.908, 0.944, 0.903, and 0.913 for reservoir, conduit, contractile strain and V_{max}, V_p, V_{min}, respectively. Regarding interobserver variability, ICC for reservoir, conduit, contractile strain and V_{max}, V_p, V_{min} were 0.974, 0.932, 0.898, 0.931, 0.899 and 0.882, respectively.

4.1.   Comparison of the systemic sclerosis population with healthy controls

Detailed clinical and echocardiographic data of the 72 SSc patients and their comparison with healthy subjects are reported in Table 1.

Our patients and healthy controls were matched in age and gender distribution. BSA and LV EF values were significantly higher in healthy controls, but the difference was clinically not remarkable. LV EF was preserved ($\geq 55\%$) in 70 (97%), while mildly reduced (45–54%) in 2 (3%) patients. On the other hand, LV GLS was significantly reduced while left ventricular mass index (LVMi) was significantly higher in SSc patients. The grade of the mitral regurgitation and systolic pulmonary artery pressure (PASP) were similar in the two groups. Myocardial early diastolic velocity (e') was significantly lower, while mean E/e' was significantly higher in the SSc population. LV diastolic dysfunction was found in 48 (67%) patients. LA V_{max} index values were similar in the two groups, while LA V_{min} index and LA V_p index were significantly larger in SSc patients. Phasic volume indices representing the reservoir (TEF, EI) and conduit (PEF) functions showed significant impairment in the SSc group, while the volumetric parameter of the contractile function (AEF) did not differ between the two groups. All strain parameters were significantly decreased in the SSc population compared to the healthy group. Detailed description of the volumetric and strain parameters of the LA function is reported in Table 2.

Table 1. Baseline characteristics of the SSc population and comparison with healthy subjects

	Healthy volunteers (n=30)	SSc patients (n=72)	p
Clinical characteristics			
Age (y)	55.2 ± 7.0	57.1 ± 11.3	0.326
Female gender n (%)	24 (80)	66 (92)	0.096
BSA (m^2)	1.8 ± 0.2	1.7 ± 0.2	**0.032**
DcSSc n (%)		39 (54)	
Duration of the disease (y)		7.3 ± 5.9	
Comorbidities			
Systemic arterial hypertension n (%)		40 (56)	
Echocardiographic characteristics			
LV EF (%)	63.3 ± 2.5	60.1 ± 4.6	**0.001**
LV GLS (%)	-19.3 ± 1.5	-17.2 ± 2.3	**<0.001**
LVMi (g/m^2)	83.3 ± 11.6	97.0 ± 19.5	**<0.001**
Grade of mitral regurgitation			0.363
Mild n (%)	29 (97)	66 (92)	
Moderate n (%)	1 (3)	6 (8)	
Severe n (%)	0	0	
PASP (mmHg)	25.5 ± 2.8	26.6 ± 7.5	0.634
Mitral E (cm/s)	79.8 ± 13.0	73.8 ± 18.0	0.117
Mitral A (cm/s)	60.7 ± 14.3	72.4 ± 20.4	**0.002**
Mitral E/A	1.37 ± 0.3	1.1 ± 0.4	**<0.001**
Averaged mitral annular S (cm/s)	9.8 ± 1.3	8.3 ± 1.3	**<0.001**
Averaged mitral annular e' (cm/s)	10.9 ± 1.4	8.3 ± 2.0	**<0.001**
Averaged mitral annular a' (cm/s)	10.0 ± 1.6	9.8 ± 1.6	0.594
Mitral E/e'	7.4 ± 1.4	9.4 ± 2.8	**<0.001**
LV diastolic function			**<0.001**
Normal n (%)	30 (100)	24 (33)	
Impaired relaxation n (%)		23 (32)	
Pseudonormal n (%)		25 (35)	

BSA: body surface area; DcSSc: diffuse cutaneous systemic sclerosis; ACE: angiotensin-convertase-enzyme; LV: left ventricular; EF: ejection fraction; GLS: global longitudinal strain; LVMi: left ventricular mass index; PASP: systolic pulmonary artery pressure

Table 2. Volumetric and strain parameters of the LA function in SSc patients and in healthy subjects

	Healthy volunteers (n=30)	SSc patients (n=72)	p
LA volumes			
V_{max} index (ml/m^2)	24.3 ± 5.7	25.0 ± 7.7	0.649
V_{min} index (ml/m^2)	9.2 ± 3.0	11.8 ± 5.2	**0.003**
V_p index (ml/m^2)	13.4 ± 3.7	16.2 ± 6.6	**0.010**
Phasic volume indices			
TEF (%)	62.6 ± 5.0	53.9 ± 8.9	**<0.001**
EI (%)	171.9 ± 37.0	125.2 ± 44.1	**<0.001**
PEF (%)	44.9 ± 6.8	36.5 ± 9.8	**<0.001**
AEF (%)	31.4 ± 9.1	27.4 ± 9.3	0.058
Strain parameters			
ε_R (%)	51.8 ± 7.4	41.1 ± 8.2	**<0.001**
ε_{CD} (%)	27.1 ± 4.6	22.3 ± 6.5	**0.001**
ε_{CT} (%)	24.8 ± 4.9	18.8 ± 4.1	**<0.001**

LA: left atrium; V_{max}: maximal volume; V_{min}: minimal volume; V_p: volume at the beginning of P wave; TEF: total emptying fraction; EI: expansion index; PEF: passive emptying fraction; AEF: active emptying fraction; ε_R: reservoir strain; ε_{CD}: conduit strain; ε_{CT}: contractile strain

4.2. Worsening of strain and volumetric parameters parallel with the decline of the left ventricular diastolic function

SSc patients were subgrouped according to the LV diastolic function: 24, 23 and 25 patients had normal relaxation, impaired relaxation and pseudonormal pattern, respectively. None of the patients had restrictive pattern.

Duration of the SSc was significantly longer in patients with pseudonormal pattern compared with the other two groups. Normal LV diastolic function was found in all healthy persons. Patients with normal relaxation were significantly younger, while patients with LV diastolic dysfunction were significantly older than our healthy subjects. LV EF was significantly higher in healthy controls compared with SSc patients with LV diastolic dysfunction. This difference, however, was clinically not remarkable. LV GLS was already significantly reduced in SSc patients with normal relaxation and showed further decline in patients with pseudonormal pattern. In addition, LVMi was significantly higher in patients with LV diastolic dysfunction. Reservoir strain values were significantly lower in all SSc subgroups than those in healthy subjects. No significant difference was found between reservoir strain values of patients with normal and impaired relaxation. On the contrary, conduit strain was preserved in SSc patients with normal LV relaxation while reduced in both groups with LV diastolic dysfunction.

Contractile strain values were significantly lower in all SSc subgroups than those in healthy subjects. Nevertheless, significantly higher contractile strain values were measured in the impaired relaxation subgroup compared with the other two SSc subgroups (Figure 1A).

All LA volumes became significantly higher in the pseudonormal group only. TEF and EI, as parameters of LA reservoir function, and PEF as parameter of conduit function showed similar behavior as reservoir and conduit strain, respectively. The differences between the groups, however, were not always statistically significant. Regarding AEF - the parameter of contractile function - the differences between groups were not significant (Figure 1B).

4.3. Parameters of left atrial size and function: comparison of their diagnostic power in predicting elevated left ventricular filling pressure

Elevated NT-proBNP levels (> 220 pg/ml) were found in 21 (29%) patients. Characteristics of our study cohort stratified by this NT-proBNP value are shown in Table 3.

Patients with elevated NT-proBNP levels were significantly older and their walking distance was significantly shorter compared with the other subgroup. The course of the SSc was significantly longer in this population. The difference in LV EF was clinically not remarkable. Significantly higher E/e' values were found in the patients with elevated NT-proBNP levels: E/e' > 14 was found in 5 (24%) patients, while in 10 (48%) patients E/e' values were in the "grey zone" (between 10 and 14) in this subgroup. LA V_{max} index and reservoir strain were similar in the two subgroups. LA stiffness, on the other hand, was significantly elevated in the subgroup of patients with high NT-proBNP values.

In stepwise multiple linear regression analysis eGFR, LA stiffness and LV EF became independent predictors of the NT-proBNP level (multiple r=0.614; p=0.000; F=13.537). VIF values for all variables were below 2.5.

Using ROC analysis, LA stiffness showed the highest diagnostic performance in predicting NT-pro-BNP > 220 pg/ml, with an AUC of 0.719. ROC curves demonstrating the predictive power of the three LA parameters are presented in Figure 2.

Sensitivity and specificity values were computed for LA stiffness using various possible cut-off points (Figure 3). LA stiffness with the cutoff value of 0.314 showed a high specificity (89.4 %) in predicting NT-pro-BNP > 220 pg/ml, with a sensitivity of 42.1%.
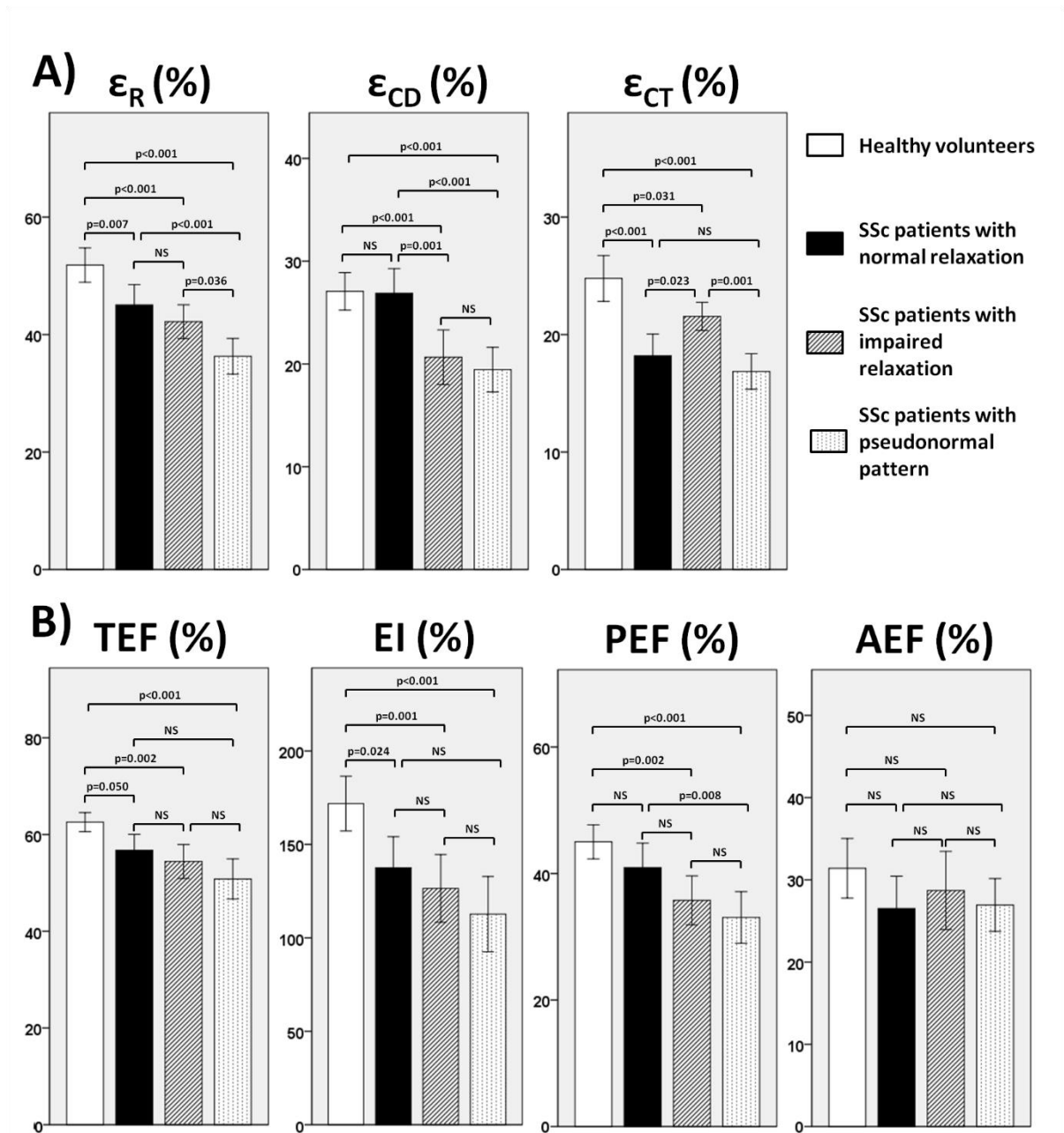
Figure 1. Progression of strain (A) and phasic volume indices (B) parallel with the worsening of the LV diastolic function in SSc patients and comparison with the parameters of healthy subjects

Table 3. Characteristics of the study population stratified by the NT-proBNP cut-off

|	All SSc patients (n=72)	NT-proBNP ≤ 220 pg/ml (n=51)	NT-proBNP > 220 pg/ml (n=21)	p
Clinical characteristics				
Age (y)	57.1 ± 11.3	54.5 ± 11.7	63.2 ± 7.3	**<0.001**
Female gender n (%)	66 (92)	46 (90)	20 (95)	0.482
BMI (kg/m^2)	25.9 ± 5.0	26.3 ± 4.7	25 ± 5.7	0.328
BSA (m^2)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.933
DcSSc n (%)	39 (54)	25 (49)	14 (67)	0.172
Duration of the disease (y)	7.3 ± 5.9	6.3 ± 5.3	9.7 ± 6.8	**0.031**
NYHA class				0.080
Class I n (%)	22 (31)	17 (33)	5 (24)	
Class II n (%)	32 (44)	25 (49)	7 (33)	
Class III n (%)	18 (25)	9 (18)	9 (43)	
6MWT distance (m)	396 ± 94	410 ± 96	360 ± 83	**0.041**
eGFR (ml/min/1.73m^2)	87.3 ± 24.6	94.4 ± 21.6	70.1 ± 23.0	**<0.001**
NT-proBNP (pg/ml)	181.4 ± 153.9	97.6 ± 44.7	384.7 ± 133.2	**<0.001**
Echocardiographic characteristics				
LV EF (%)	60.1 ± 4.6	61.6 ± 3.4	59.1 ± 5.5	**0.039**
LVMi (g/m^2)	97.0 ± 19.5	95.8 ± 21.3	99.7 ± 14.4	0.370
Grade of mitral regurgitation				**0.035**
Mild (n) %	66 (92)	49 (96)	17 (81)	
Moderate (n) %	6 (8)	2 (4)	4 (19)	
Severe (n) %	0	0	0	
PASP (mmHg)	26.7 ± 7.5	25.3 ± 5.7	29.6 ± 10.1	0.062
Mitral E (cm/s)	73.8 ± 18.0	72.0 ± 16.5	78.3 ± 21.1	0.187
Mitral A (cm/s)	72.4 ± 20.4	67.9 ± 17.6	84.1 ± 22.5	**0.002**
Mitral E/A	1.1 ± 0.4	1.1 ± 0.4	0.95 ± 0.2	**0.020**
Averaged mitral annular S (cm/s)	8.3 ± 1.3	8.4 ± 1.2	8.0 ± 1.5	0.218
Averaged mitral annular e' (cm/s)	8.3 ± 2.0	8.6 ± 2.1	7.5 ± 1.6	**0.040**
Averaged mitral annular a' (cm/s)	9.8 ± 1.6	9.9 ± 1.6	9.5 ± 1.6	0.295
Mitral E/e'	9.4 ± 2.8	8.7 ± 2.3	11.0 ± 3.4	**0.001**
LA parameters				
V_{max} index (ml/m^2)	25.0 ± 7.7	24.7 ± 7.8	25.6 ± 7.7	0.672
V_{min} index (ml/m^2)	11.8 ± 5.2	11.5 ± 4.7	12.4 ± 6.3	0.474
V_p index (ml/m^2)	16.2 ± 6.6	16.0 ± 6.3	16.7 ± 7.3	0.701
ε_R (%)	41.1 ± 8.2	41.9 ± 8.1	39.0 ± 8.2	0.178
ε_{CD} strain (%)	22.3 ± 6.5	22.8 ± 6.7	20.9 ± 5.8	0.218
ε_{CT} strain (%)	18.8 ± 4.1	19.1 ± 4.2	18.1 ± 3.9	0.372
Stiffness	0.245 ± 0.12	0.219 ± 0.08	0.311 ± 0.16	**0.024**

Abbreviations as in Tables 2 and 3.
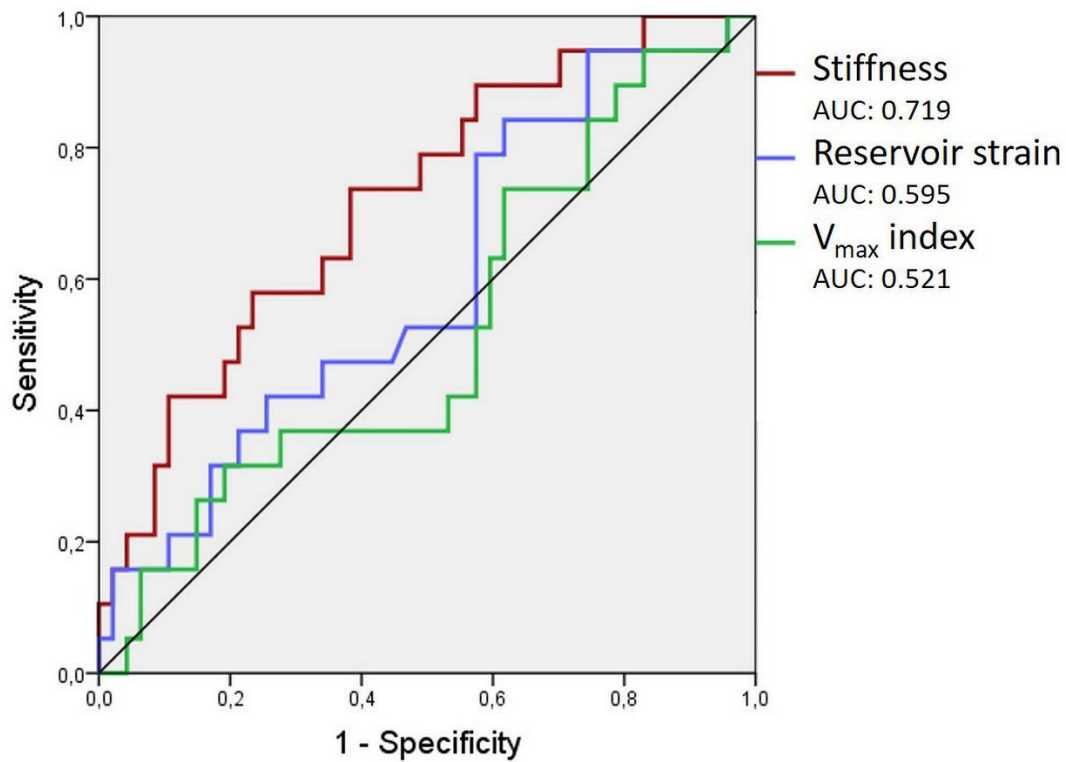
Figure 2. ROC curves for maximal LA volume index, LA reservoir strain and LA stiffness for the prediction of NT-proBNP > 220 pg/ml
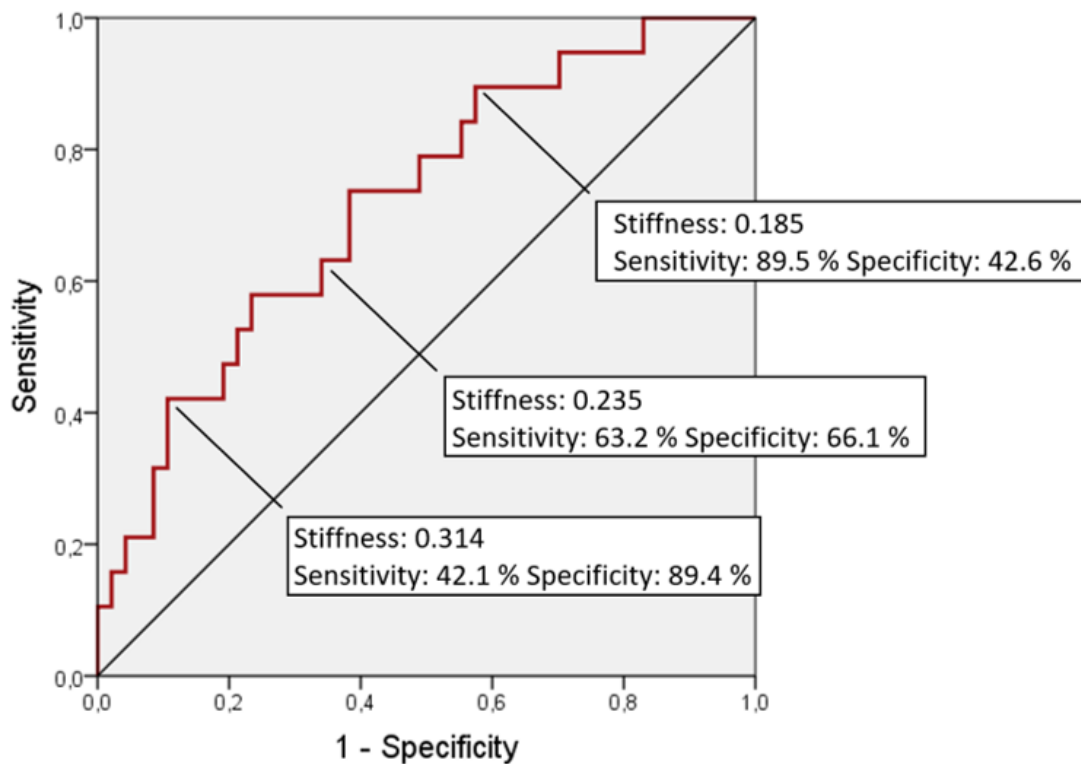

Figure 3. ROC curve displaying the sensitivity and specificity of various LA stiffness values in predicting NT-proBNP > 220 pg/ml

5. DISCUSSION

In SSc, LV diastolic dysfunction and the consequential HFpEF are reported to be frequent as they reflect the primary myocardial involvement of the disease. Therefore, we considered this population as a representative model to investigate the changes in LA size and mechanics parallel with the progression of LV diastolic dysfunction, by the help of volumetric and 2D STE–derived strain techniques.

Our results suggest that LV diastolic function has a strong impact on LA size and mechanics in SSc: Because the proportion of patients with normal or impaired LV relaxation was high in our study, the average values of LA V_{max} index were similar in our SSc patients and healthy population. In patients with pseudonormal pattern, however, significantly higher LA V_{max} index values were found. Similarly, LA V_{min} and V_p index values were significantly higher in the subgroup of SSc patients with pseudonormal pattern. Even in this subgroup, however, the average value of LA V_{max} index does not completely fulfill the criteria declared in the current guideline (LA V_{max} index > 34 ml/m^2), but because the high specificity and low sensitivity of this cut-off value is well known, we consider the higher V_{max} index to be a sign of elevated LV filling pressure.

STE-derived strain data suggested that LA reservoir and contractile function already showed significant worsening in SSc patients with preserved LV diastolic function, compared with the healthy subjects, whereas LA conduit function was preserved in this early phase of the disease. LA conduit function started to decline in patients with impaired relaxation, whereas further deterioration of the LA reservoir function was pronounced in the pseudonormal group only. On the other hand, LA contractile function increased significantly in the impaired relaxation group compared with the preserved LV diastolic function group and then significantly decreased with further worsening of the LV diastolic function. This latter finding is in line with previous reports suggesting that LA contractile function increases in the presence of mild LV diastolic dysfunction, according to the Frank-Starling law, which becomes hardly effective at end-stage ventricular diastolic dysfunction when the limits of the atrial preload reserve are reached.

LA V_{max} index is mentioned in the recent guideline as a useful marker for identification of LV diastolic dysfunction. Our data suggest, however, that enlargement of the LA V_{max} index appears only late in the course of the disease, whereas pathologic processes may be revealed much earlier with the help of the parameters of LA mechanics.

Early and reliable detection of LV diastolic dysfunction and elevated filling pressure has important diagnostic and prognostic implications in heart failure. Nowadays, therefore there is

a continuing search for non-invasive markers. E/e′ is one of the most studied parameter. It provides a close approximation of LV filling pressures in a wide spectrum of diseases and its prognostic value has also been proved. Nevertheless, strength of correlation between E/e′ and LV filling pressure varied widely between studies. Particularly weak correlations were observed in the so called grey zone (average E/ e′ between 10 and 14; septal E/e′ between 8 and 15; lateral E/e′ between 8 and 12).

LA V_{max} index has been reported as a useful biomarker of the severity and duration of the elevated LV filling pressure. Thus the current recommendations suggest the use of LA V_{max} index as additional parameter for the evaluation of LV filling pressure.

Recent studies in line with our results proved, however, that the enlargement of the cavity is preceded by the functional remodelling of the LA. 2D STE-derived LA reservoir strain showed a good correlation with the invasively measured LV filling pressure, exceeding the diagnostic power of the LA V_{max} index.

Beside LA reservoir strain, we applied a further parameter of the atrial performance, LA stiffness, which has never been investigated in SSc before. This parameter is obtained by TDI and speckle tacking techniques and represents the change in pressure required to increase the volume of the atrium in a given measure. Kurt et al. reported LA stiffness as a useful index to differentiate between HFpEF and asymptomatic diastolic dysfunction.

Thus we aimed to compare the diagnostic power of LA V_{max} index, LA reservoir strain and LA stiffness in predicting elevated LV filling pressure in SSc patients. Because of the above-mentioned inaccuracies of E/e', in this study we used NT-proBNP as non-invasive measure of the LV filling pressure. NT-proBNP > 220 pg/ ml is considered to have a high positive predictive value for the diagnosis of HFpEF, therefore we applied this cut-off as a non-invasive indicator of elevated LV filling pressure.

Our data show that LA stiffness has higher discriminative strength in identifying patients with elevated NT-proBNP levels compared with LA V_{max} index and LA reservoir strain. Two parameters, both reflecting LV filling pressure but obtained by completely different approaches, are combined in LA stiffness. This may explain the diagnostic efficacy of this parameter.

The common principle of the previous and current echocardiographic recommendations is that cut-off values with high specificity are used to avoid false positive diagnoses of diastolic dysfunction and elevated filling pressure. Thus we suggest the use LA stiffness with the cut-off value of 0.314 as this value showed high specificity (with modest sensitivity) in predicting elevated LV filling pressures.

6. CONCLUSION

The main finding of our study is that LA mechanics strongly reflects the changes in LV diastolic function in SSc: LA reservoir and conduit function decline parallel with the deterioration of the LV diastolic function while enhanced contractile function in the early stage of the LV diastolic dysfunction demonstrates the compensatory behavior of the LA. 2D STE is a well reproducible, robust technique for tracking of these changes in the LA mechanics. Phasic volume indices, on the other hand, are less useful in depicting these processes.

Strain parameters of LA reservoir and contractile function already show significant worsening in SSc patients with preserved LV diastolic function, suggesting that impairment of LA mechanics is an early sign of myocardial involvement in SSc, which appears earlier in the course of the disease than the conventional signs of LV diastolic dysfunction.

LA stiffness was superior to LA V_{max} index and LA reservoir strain in predicting elevated NT-proBNP levels in our SSc patients. Although invasive validation studies on larger samples are required, our data suggest, that the use of LA stiffness may significantly contribute to diagnostic precision in populations with a high suspicion of HFpEF.

In conclusion, our data suggest that LA strain and stiffness may provide additional information regarding early myocardial involvement of the disease, LV diastolic dysfunction and elevated LV filling pressure. Thus their measurement may be included in the non-invasive follow-up of the SSc patients.

7. NOVEL FINDINGS

- Strain parameters of the LA mechanics strongly reflect the changes in LV diastolic function in SSc.
- LA reservoir and contractile strain already show significant worsening in SSc patients with preserved LV diastolic function, suggesting that impairment of LA mechanics is an earlier sign of the myocardial involvement in this disease than the conventional echocardiographic parameters of the LV diastolic dysfunction.
- LA stiffness is superior to maximal LA volume index and LA reservoir strain in predicting elevated NT-proBNP levels in SSc patients. The use of LA stiffness may significantly contribute to the diagnostic precision in recognizing elevated LV filling pressure in this population.

8. BIBLIOGRAPHY OF THE AURTHOR'S PUBLICATIONS

8.1.　Publications related to the thesis

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8.2. Publications not related to the thesis

Full papers

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9. ACKNOWLEDGEMENT