LEFT ATRIAL MECHANICS IN SYSTEMIC SCLEROSIS

PhD thesis

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1. ABBREVIATIONS

2D:	2-dimensional
3D:	3-dimensional
6MWT:	six-minute walk test
A:	late diastolic velocity of the mitral inflow
a':	late diastolic myocardial longitudinal velocity
ACR/EULAR:	American College of Rheumatology/ European League Against Rheumatism
ACE:	angiotensin-converting enzyme
ASE/EACVI:	American Society of Echocardiography/European Association of Cardiovascular Imaging
AUC:	area under the curve
BSA:	body surface area
BMI:	body mass index
CT:	computed tomography
DcSSc:	diffuse cutaneous form of systemic sclerosis
DT:	deceleration time
E:	early diastolic velocity of the mitral inflow
e':	early diastolic myocardial longitudinal velocity
EF:	ejection fraction
eGFR:	estimated glomerular filtration rate
GLS:	global longitudinal strain
ε_R:	reservoir strain
ε_{CD}:	conduit strain
ε_{CT}:	contractile strain
HF:	heart failure
HFpEF:	heart failure with preserved ejection fraction
ICC:	intra-class correlation coefficient
LA:	left atrium
LV:	left ventricle
LVMi:	left ventricular mass index
M-mode:	motion mode
MANOVA:	multivariate analysis of variance
MRI:	magnetic resonance imaging
NT-proBNP:	N-terminal pro-B-type natriuretic peptide
NYHA:	New York Heart Association
ROC curve:	receiver operating characteristic curve
PAH:	pulmonary arterial hypertension
PASP	pulmonary artery systolic pressure
PCWP:	pulmonary capillary wedge pressure
S:	systolic myocardial longitudinal velocity
SD:	standard deviation
SSc:	systemic sclerosis
STE:	speckle tracking echocardiography
TDI:	tissue Doppler imaging
VIF:	variance inflation factor

2. 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[1], and may represent a diagnostic challenge: Left ventricular (LV) systolic dysfunction is rare in SSc[2], but diastolic dysfunction and the consequential heart failure with preserved ejection fraction (HFpEF) are much more frequent.[3–5] They reflect the primary myocardial involvement of the disease.[1] 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.[6–9] 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.[10–12] Increasing number of studies have emphasized the importance of LA dysfunction in the pathophysiology of HFpEF.[9,13] 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.[14,15] The impact of LV diastolic function on the volumetric and strain derived parameters of LA function has already been reported in the general population.[16,17] 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.[18,19] It was reported as a useful index to distinguish HFpEF patients from those with asymptomatic diastolic dysfunction.[19]

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

3. 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.

4. BACKGROUND

4.1. Cardiac complications in systemic sclerosis

SSc is a systemic connective tissue disease, characterized by inflammation, microvascular damage and generalized fibrosis in multiple organs. Cardiac involvement in SSc was first described in 1926 by Heine, who found pathological changes in the myocardium, pericardium and coronary arteries during an autopsy of a SSc patient.[20] Since then it has been proved that cardiac manifestation is present in a high proportion of patients though it is often clinically asymptomatic.[1] While its estimated clinical prevalence is about 15–35%, at post-mortem studies cardiac involvement was found in up to 80 % of the patients.[21] The development of overt myocardial manifestations is recognized as powerful adverse prognostic factors and may affect patients with both limited cutaneous SSc and diffuse cutaneous SSc.[21] Epidemiologic studies emphasize that cardiac involvement is responsible for 20%–30% of all premature deaths in SSc.[22] Cardiac manifestations may affect all structures of the heart: pericardial effusion, arrhythmias, conduction system abnormalities, myocardial ischemia, myocardial hypertrophy and HF may all occur.[1,23] While LV systolic dysfunction is not common in SSc[2], LV diastolic dysfunction and the consequential HFpEF are much more frequent.[3,5] As the disease progresses, permanent structural abnormalities of the small coronary arteries may result in reduced coronary flow reserve which leads to myocardial microcirculation disturbances.[24–26] Repeated ischemia, collagen overproduction, and complex immune system dysregulation lead to ischemic, fibrotic, and inflammatory lesions involving the myocardium.[27] These processes may ultimately lead to myocardial fibrosis, which is the pathologic hallmark of cardiac involvement in SSc.[1] Many studies demonstrated that the primary myocardial manifestation of the disease is LV diastolic dysfunction as a result of irreversible myocardial fibrosis. If myocardial fibrosis progresses, diastolic compliance of the LV decreases and manifest HFpEF may evolve. Numerous characteristic symptoms of SSc patients (impaired functional capacity, dyspnea, peripheral oedema) are definitely related to LV diastolic dysfunction and elevated filling pressure. HF symptoms in SSc, however, may be misinterpreted as PAH or interstitial lung disease, leaving HFpEF underdiagnosed. Apparent myocardial manifestations increase the risk of clinical deterioration and mortality[3,4,28], therefore monitoring of myocardial involvement represents an important aspect of SSc management.[1] Early and reliable detection of diastolic dysfunction and increased filling pressure is crucial for preventing the development of cardiac

symptoms, improving the quality of life and reducing the mortality. Thus, screening for markers of cardiac dysfunctions is known to be beneficial. Annual echocardiography and/or evaluation of NT-proBNP concentrations should be carried out in all SSc patients to rule out PAH. Moreover, analysis of NT-proBNP allows the detection of numerous cardiac involvements, including LV systolic and diastolic dysfunction and consequential HF in SSc.[29,30] Besides its diagnostic value, it also appears to be a reliable and independent predictor of cardiovascular and all-cause mortality in this disease.[31,32]

During echocardiography close attention should be also paid to recognize the early signs of LV diastolic dysfunction. Although there is limited evidence in respect of specific therapeutic options, treatment of early abnormalities with calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors may improve myocardial perfusion and function.[1,33] However, it remains to be seen if early intervention can limit the progression of these life-threatening complications.[23]

4.2. Echocardiographic evaluation of left ventricular diastolic dysfunction and elevated filling pressure

The assessment of diastolic function has become particularly relevant, as in the general population approximately half of patients with HF have normal ejection fraction (HFpEF)[34], a condition in which diastolic dysfunction is thought to be the hallmark pathophysiological process.[35]

Echocardiography plays a central role in the assessment of LV diastolic function and LV filling pressures. Whereas LV systolic function is routinely quantified by measuring ejection fraction (EF) or deformation parameters such as global longitudinal strain (GLS), there is no single echocardiographic measure that quantifies LV diastolic function. By using a combination of different echocardiographic indices, diastolic performance may be reasonably estimated in most patients, however it still may be a challenging task in the everyday practice.

Echocardiographic evaluation of diastolic function has been traditionally performed by measurement of transmitral flow parameters including the early (E) and late (A) diastolic filling velocities, the E/A ratio, the deceleration time (DT) of the E wave and the isovolumetric relaxation time (IVRT) from an apical four-chamber view with conventional pulsed wave Doppler.[36] Mitral inflow velocities have been used to define LV filling patterns as normal, impaired relaxation, pseudonormal, and restrictive filling. The transmitral flow parameters have

been shown to be reliable in patients with LV systolic dysfunction.[37,38] In patients with preserved ejection fraction, however, these parameters do not always correlate with LV filling pressure.[39–41] In addition, parameters of the transmitral flow may vary with age and heart rate. As LV stiffness progresses, LA pressure increases to maintain the transmitral pressure gradient. During this process, E/A ratio will temporarily normalize, despite the presence of moderately severe disease. This is referred as pseudonormalization and highlights a limitation to the sole use of E/A ratios for diagnosis. To overcome these limitations, combinations of the mitral inflow velocity curves with the pulmonary venous flow curves[42] and the response of the mitral inflow to altered loading conditions (e. g. Valsalva maneuver) have been used[43], until the introduction of tissue Doppler imaging (TDI) technique.

If measured on the mitral annulus, tissue Doppler-based early diastolic myocardial longitudinal velocity (e′) is strongly related to ventricular relaxation, and less load dependent than the transmitral flow velocities.[44,45] Invasive studies have demonstrated that the e' velocity correlates inversely with the time constant of LV relaxation (tau).[46] Similarly to the transmitral flow velocities, age-associated changes have been observed in e' value and its accuracy is also angle-dependent.[47,48]

Since e′ is primarily a measure of early diastolic relaxation, and the E wave reflects the early diastolic LA to LV pressure gradient (and therefore affected by both LA pressure and LV early diastolic relaxation), the ratio of E/e' provides an estimate of LA pressure.[40] Regarding the non-invasive estimation of LV filling pressure, it is the most thoroughly studied index and is included into the algorithms of all the relevant authoritative documents.[6,49,50] E/e′ 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 clinical trials. In addition, recent studies have challenged the accuracy of E/e′ in patients with or at risk for HFpEF.[7,51–54] Particularly weak correlations were observed in the so called grey zone (average E/ e′ between 10 and 14[6]; septal E/e′ between 8 and 15[40]; lateral E/e′ between 8 and 12[55]).

The new 2016 EACVI/ASE recommendations advise four variables for diagnosing diastolic dysfunction and elevated filling pressure: annular e' velocity, average E/e' ratio, maximal LA volume index, and peak tricuspid regurgitation velocity.[6] In addition, structural changes (e.g., LV hypertrophy) may indicate abnormalities of diastole and should be also considered.[56]

By using a combination of different echocardiographic indices, diastolic performance may be estimated. Nevertheless, all the recently used parameters have limitations and their diagnostic accuracy and sensitivity to detect early alterations may still not be reliable enough.

Therefore, there is still a continuing search for additional echocardiographic parameters for identifying the early stages of LV diastolic dysfunction as well as the elevated LV filling pressure. Nowadays, there is more and more attention is focused towards the volumetric and even more towards the functional parameters of the LA, since they may represent the missing additional value in the echocardiographic analysis of LV diastolic dysfunction and elevated LV filling pressure.

4.3. Echocardiographic assessment of left atrial size

During the era of M-mode studies, the size of LA was measured using its antero-posterior diameter in the parasternal long axis view.[57] In the Framingham population, LA size obtained by M-mode, was proved to be one of the predictors of atrial fibrillation.[58] Despite its high reproducibility, antero-posterior diameter is considered inaccurate because it does not reflect the real LA size: Due to the effect of surrounding structures in the chest, dilation of the LA is not equal in all dimensions, but predominantly affects supero-inferior and medio-lateral directions.[59] The 2D option for estimating LA size is LA area obtained in apical two- or four-chamber views, but this technique is barely used in common practice.

Current guidelines recommend the use of LA volumes both in research and in everyday practice.[60] LA volume has a higher prognostic value than antero-posterior diameter or LA area because it barely relies on geometric assumptions and permits to detect dilatation along different space axes. The American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) recommend the assessment of LA volume by 2D echocardiography in apical two- and four-chamber views with Simpson's method or biplane area-length method.[60] LA volume parameters obtained by this technique show much closer correlation with the gold standard cardiac magnetic resonance imaging (MRI) results than the diameter or area values.[61] This correlation was further enhanced by the introduction of 3D echocardiography, which does not require any geometric assumption.[60] Unfortunately, this technique is dependent on image quality and has lower temporal resolution.[62] Several studies, however, indicate that both 2D and 3D echocardiography underestimate the LA volume significantly when compared to cardiac MRI or CT.[63–65] Body size significantly determines LA volumes, even in a healthy population. Therefore, in practice, normalization of LA volume parameters to body surface area (BSA) is recommended (LA volume index).[60] The normal range of LA volume index as measured by echocardiography is 22 ± 6 ml/m^2.[66]

4.4. Left atrial phasic function

One of the most fundamental roles of LA is to optimize LV filling and cardiac output. Its function has been conventionally divided into three phases. The introduction of non-invasive imaging modalities, such as 2D and 3D echocardiography, STE and cardiac MRI has significantly contributed to our understanding of the LA phasic functions: The *reservoir phase* starts with mitral valve closure: the LA fills up due to the downward movement of the mitral annulus toward the apex, as a result of LV contraction. As LA pressure falls, its volume increases facilitating the passage of blood from the pulmonary veins. After mitral valve opening, in early diastole, the blood stored in the LA passively enters the LV due to its suction effect and LA acts as a 'conduit' between pulmonary veins and the LV (*conduit phase*). Finally, in the *contractile phase,* at late diastole, LA contracts and further fills the LV. [66] In patients with normal diastolic function, the three phases account for about 40%, 35%, and 25% of LV filling, respectively.[67]

4.5. Echocardiographic assessment of left atrial function

Over the last decades, various methods were applied to assess LA function with more or less success. The late diastolic myocardial longitudinal velocity (a') measured on the mitral annulus using TDI is considered as a LA functional parameter. It was proved that a' shows good correlation with NT-proBNP levels in hypertrophic cardiomyopathy[68], still it has not become a routinely used method.

4.5.1. Phasic volume indices of the left atrium

LA function may be evaluated by measuring LA volumes in different time points during the cardiac cycle (V_{max}, V_{min}, V_p). With this approach phasic volume indices may be calculated reflecting reservoir, conduit and contractile function. TEF and EI have been assumed to reflect LA reservoir function and AEF and PEF to reflect LA contractile and conduit function, respectively.[69] (**Table 1.**)

- Reservoir function:
  - V_{te} index = total emptying volume index= (V_{max} - V_{min})/BSA
  - TEF = total emptying fraction= emptying volume/ V_{max} x 100 (%)
  - EI = expansion index = emptying volume/ V_{min} x 100 (%)

- Conduit function:
  - V_{pe} index= passive emptying volume index = (V_{max} - V_p)/BSA
  - PEF =passive emptying fraction = passive emptying volume/ V_{max} x 100 (%)

- Contractile function:
  - V_{ae} index = active emptying volume index = (V_p - V_{min})/BSA
  - AEF = active emptying fraction = active emptying volume/Vp x 100 (%)

Table 1. Calculation of phasic volume indices

4.5.2. Two-dimensional speckle tracking-derived strain analysis

Assessment of atrial deformation by tissue Doppler-derived strain imaging was proposed as an alternative method for evaluation of LA function.[70] However, this approach had several disadvantages, including suboptimal reproducibility, angle dependence and the confounding effect of artefacts.[14,71]

2D-STE, however, eliminated the majority of these disadvantages. This novel method for real-time quantitative assessment of myocardial function and deformation detects multiple unique patterns and natural acoustic reflections described as “speckles”, by using conventional gray scale 2D echocardiography. Speckle formations are generated by the interference of the ultrasound beams in the myocardium and serve as tissue markers that may be tracked frame-by-frame. Each myocardial region has a unique speckle pattern, like a fingerprint. This provides local myocardial displacement information, which can be utilized for the calculation of strain. Originally it was used to detect the subclinical impairment of LV function (global longitudinal strain- GLS). Later this technique was also applied for the assessment of the mechanics of other cardiac chambers, such as LA.

After the acquisition of atrial 2D images in apical four- and two-chamber views, strain curves are obtained by a specific offline semiautomated software. Good image quality and relatively high frame rate (50-70 frames/sec) are necessary for accurate tracking.[14,15] Recommendations advise to use the QRS complex in the ECG as the zero reference point of the analysis.[72] LA strain profiles represent three phases of the LA function: the peak of the positive longitudinal atrial strain, after the QRS complex corresponds to reservoir function (reservoir strain- ε_R). The

late diastolic strain wave (contractile strain- ε_{CT}) point to atrial booster pump function. The conduit strain (ε_{CD}) is defined as the difference between the ε_R and the ε_{CT}.[72] (**Figure 1.**)

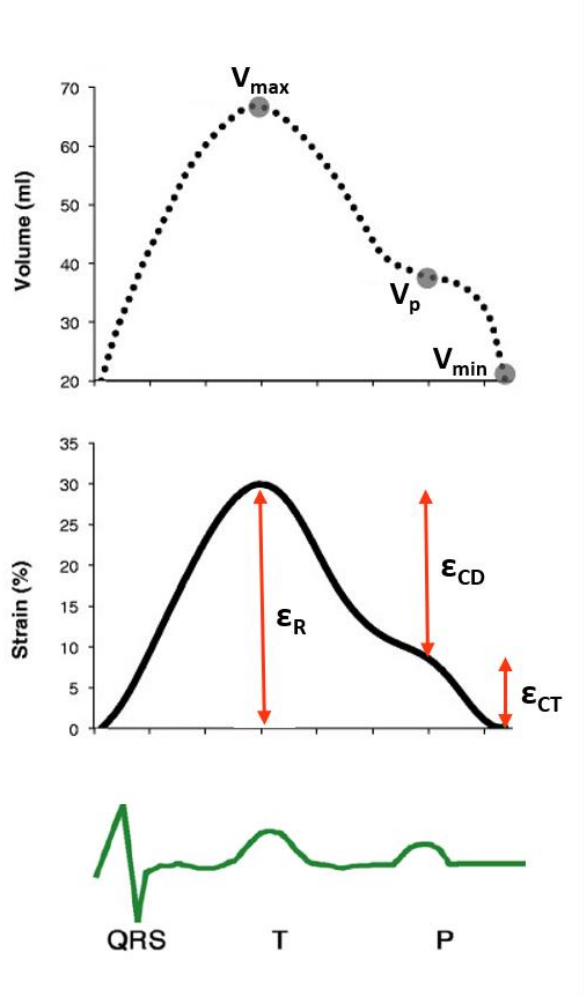

Figure 1. Schematic picture of atrial volume and strain curves

(V_{max}: maximal volume; V_{min}: minimal volume; V_p: volume at the beginning of P wave; ε_R: reservoir strain; ε_{CD}: conduit strain; ε_{CT}: contractile strain)

The use of STE for the assessment of LA mechanics has numerous advantages: it is a quantitative method, with wide availability, independent of angle, less affected by tethering from neighbouring segments, relatively independent of loading conditions and geometric assumptions, with very low intraobserver and interobserver variability.[14,15,66] LA strain may also offer technical advantages compared to other indices, particularly in patients where annular motion is altered, such as with pacing, bundle branch block and mitral annular calcification.[9] The main disadvantage of STE is the dependency on high quality images, which sometimes cannot be guaranteed in patients with limited acoustic windows, due to the far-field location of the LA.

4.5.3. Left atrial stiffness

LA stiffness is a further parameter of the atrial performance. Stiffness represents the change in pressure required to increase the volume of the atrium in a given measure.[18,19] It is a dimensionless parameter, derived from the slope of the pressure-strain relationship.[73] Using this concept, Kurt et al. proposed that stiffness may be measured invasively as the ratio of pulmonary capillary wedge pressure (PCWP) and LA ε_R. They also proposed a non-invasive method for calculating LA stiffness, where E/e′ is used as an estimate of PCWP[19]:

$$\text{LA stiffness} = \frac{\text{PCWP}}{\varepsilon R} = \frac{\text{E/e'}}{\varepsilon R}$$

Since it combines LA function evaluated through STE and the Doppler estimate of end-diastolic pressure; it can be considered as a marker of atrial-ventricular interplay. It was reported as a useful index to distinguish HFpEF patients from those with asymptomatic diastolic dysfunction.[19] However, further studies are needed to validate its prognostic importance in different clinical settings.

4.6. Left atrial volume and function in left ventricular diastolic dysfunction and elevated filling pressure

For a long period of time, in HF patients, attention has been focused on LV structure, dimensions and function, placing the LA to a marginal position. Recently, however, LA has acquired increasing attention and its fundamental role has been shown both in modulating ventricular filling and in providing diagnostic and prognostic information. It has become evident, that parallel with the progression of HF, LA also undergoes structural and functional alterations. Consequently, LA is capable to provide adequate LV filling even in advanced stages of LV diastolic dysfunction, while at the same time protects the pulmonary circulation from the increased backward pressure.[74] There is a growing evidence that loss of this function actively contributes to the onset of typical symptoms[75,76] and disease progression of HF.[66,77] During diastole, LA is directly exposed to the influence of LV pressure. The progression of diastolic dysfunction and the consequential increase in LV filling pressure leads to the remodelling of the LA. The most apparent change is the increase in the LA size. Evidently, LA enlargement may be the consequence of several other factors, such as mitral regurgitation, atrial fibrillation,

high cardiac output states, athlete's hearts, age and obesity.[6] In the lack of these factors, however, it is mostly related to elevated filling pressures.[74] It has been widely demonstrated, that increased LA volume is an expression of duration and severity of increased LA pressure.[78,79] According to the famous metaphor by P. S. Douglas, LA volume reflects long-standing elevated LV filling pressure, similarly to the glycated haemoglobin (HbA1c) in diabetes, whereas Doppler parameters (E/A, E/e') reflect only the actual pressure conditions similarly to blood glucose.[80]

When indexed to BSA, maximal LA volume is an independent predictor of adverse cardiovascular outcome in the general population[81] and in SSc[3]. Patients with enlarged LA show higher risk for developing HF[82] and LA V_{max} index is a robust marker of poor prognosis in patients with chronic HF.[83–85] Increased LA volume is also known as an independent predictor of raised NT-proBNP levels in HFpEF patients.[86]

Thus, the current recommendation of the ASE/EACVI suggests the use of LA V_{max} index as additional parameter for the evaluation of LV filling pressure.[6] The cut off value of LA V_{max} index is 34 ml/m ²(normal value + 2 SD), which is a highly specific but less sensitive value for the detection of elevated LA pressure.[87] Alternative diagnostic algorithms, however, also mention the value of 28 ml/m ²(normal value + 1SD), which is considered as a more sensitive cut-off.[55,87,88]

Although the diagnostic power of the LA V_{max} index is highly supported by wide-ranging literature, other data suggest that the correlation between minimal LA volume index and the LV filling pressure may be even closer.[89] Although LA V_{max} index is associated with the severity of diastolic dysfunction it should be noted that in the early stages (impaired relaxation) it is not or only slightly increased. Significantly enlarged LA is usually observed only in advanced stages of LV diastolic dysfunction (pseudonormal or restrictive filling pattern).[90]

Reduction in strain values demonstrates the microstructural remodelling that appears long before the macroscopic one. It was recently proved, that the enlargement of LA is preceded by its functional remodelling: LA function, as assessed by STE, deteriorates in the very early phase of diastolic dysfunction, before the dilation of the chamber.[17,91,92] It was proved, that asymptomatic hypertensive patients have altered LA strain despite normal LA size, that reflect preclinical LA myocardial dysfunction. Furthermore, reduced LA strain parameters are able to unmask apparently normotensive patients with hypertensive response to exercise.[93]

In a large HFpEF-population Santos et al. confirmed that LA strain is decreased independently of LA size or history of atrial fibrillation and is associated with higher prevalence of HF hospitalization.[94] In several recent studies, LA ε_R was superior to all other current

echocardiographic parameters in the evaluation of the LV filling pressures and in the diagnosis of HFpEF.[9,10,17,95,96] It was shown, that LA reservoir function closely correlates with NT-proBNP levels in HF.[97] In addition, in HFpEF patients, LA ε_R was found to be an independent predictor of exercise capacity, whereas LV mass and EF were not.[98] Besides, in HF-patients, LA ε_R was proved to be a sensitive biomarker for the prediction of adverse cardiac events independently of other echocardiographic parameters of systolic and diastolic dysfunction.[99] Thus, growing body of literature suggests focusing on the assessment of the LA phasic function rather than LA volumes only and raises the possibility that LA function may be a better diagnostic and prognostic marker than LA size in HF-patients.[100,101] Assessment of LA function by STE may represent a missing added value for a correct evaluation of patients with LV diastolic dysfunction and elevated filling pressure.

5. METHODS

5.1. Study population

Eighty consecutive patients diagnosed with SSc in the tertiary-care center of the Department of Rheumatology and Immunology, University of Pécs, were recruited for this prospective study. All enrolled cases complied with the updated American College of Rheumatology/European League Against Rheumatism classification criteria[102] and were classified as having limited cutaneous or diffuse cutaneous SSc according to the criteria described by LeRoy et al.[103] Patients with PAH, atrial fibrillation, significant left-sided valvular disease, or known coronary artery disease were excluded from the study. Detailed medical history was obtained. Duration of the disease was defined as time from the onset of the first non-Raynaud symptom of SSc to the echocardiography, in years. Limitations of physical activity were graded according to the New York Heart Association classification. Six-minute walk test (6MWT) was carried out on the same day as the echocardiographic measurements.

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. The study complied with the Declaration of Helsinki. The Institutional Ethics Committee approved the study (5338/2014). Written informed consent was obtained from all patients.

5.2. Echocardiography

Echocardiography was performed with the use of a Philips Epiq 7 ultrasound system (Philips Healthcare, Best, The Netherlands) by a single investigator. LV EF was calculated by biplane Simpson's method. End-diastolic thicknesses of the septum and the posterior wall, as well as the end-diastolic diameter of the LV were measured from the parasternal long-axis view by M-mode. LV mass was calculated according to the Devereux formula and corrected for BSA (LVM index).[60] Severity of mitral regurgitation was assessed according to the current recommendations and classified as mild, moderate, or severe.[104] In addition to the spectral Doppler parameters of the transmitral flow (E, A), myocardial systolic (S), and early (e') and late (a') diastolic velocities were measured from the apical four-chamber view at the lateral and septal borders of the mitral annulus by means of pulsed tissue Doppler imaging. Lateral and septal myocardial velocities were averaged. Mitral E/A and E/e' ratios were calculated.[6]

Pulmonary arterial systolic pressure (PASP) was estimated as a sum of the pressure difference across the tricuspid valve (calculated by means of the modified Bernoulli equation) and an estimate of mean right atrial pressure (5–15 mm Hg), calculated with the use of the diameter and collapsibility index of the inferior vena cava.[60] Doppler measurements were obtained from ≥ 3 consecutive beats.

5.3. Categorization of left ventricular diastolic function and filling pressure

LV diastolic function was evaluated in accordance with the current guideline. SSc patients were subgrouped according to the following categories[6]:
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)
E/e′ > 14 was defined as the sign of the elevated filling pressure, while values between 10 and 14 were considered as "grey zone" values.[6]

5.4. Strain measurements

For atrial speckle tracking analysis, apical four- and two-chamber view movies were obtained by means of 2D echocardiography. Care was taken to obtain true apical images with the use of standard anatomic landmarks in each view. Foreshortening was avoided, allowing a more reliable delineation of the atrial endocardial border. Three consecutive heart cycles were recorded digitally. The frame rate was set at 80–90 frames/sec. Recordings were processed offline with the use of dedicated software (QLab; Philips Healthcare, Andover, Massachusetts), by a single investigator, blinded to the echocardiographic and clinical data. In segments with poor tracking, endocardial borders were manually readjusted until better tracking was achieved. The onset of the R-wave was set as zero reference point of the strain analysis. The first positive peak of the curve was measured at the end of the reservoir phase, just before mitral valve opening (ε_R). This was followed by a plateau and a second late peak at the onset of the P-wave on the electrocardiogram (ε_{CT}). The conduit strain (ε_{CD}) was defined as the difference between the reservoir and the contractile strain **(Figure 2A)**. Results obtained in the apical four- and two-chamber views were averaged.[72]

LA stiffness was calculated as ratio of E/e′ to LA ε_R.[18,19]

With the use of the same software, LV GLS also was estimated. The LV endocardial border was carefully traced from apical four-, three- and two-chamber views to generate a composite LV strain curve. The frame rate was set at 50–55 frames/sec.

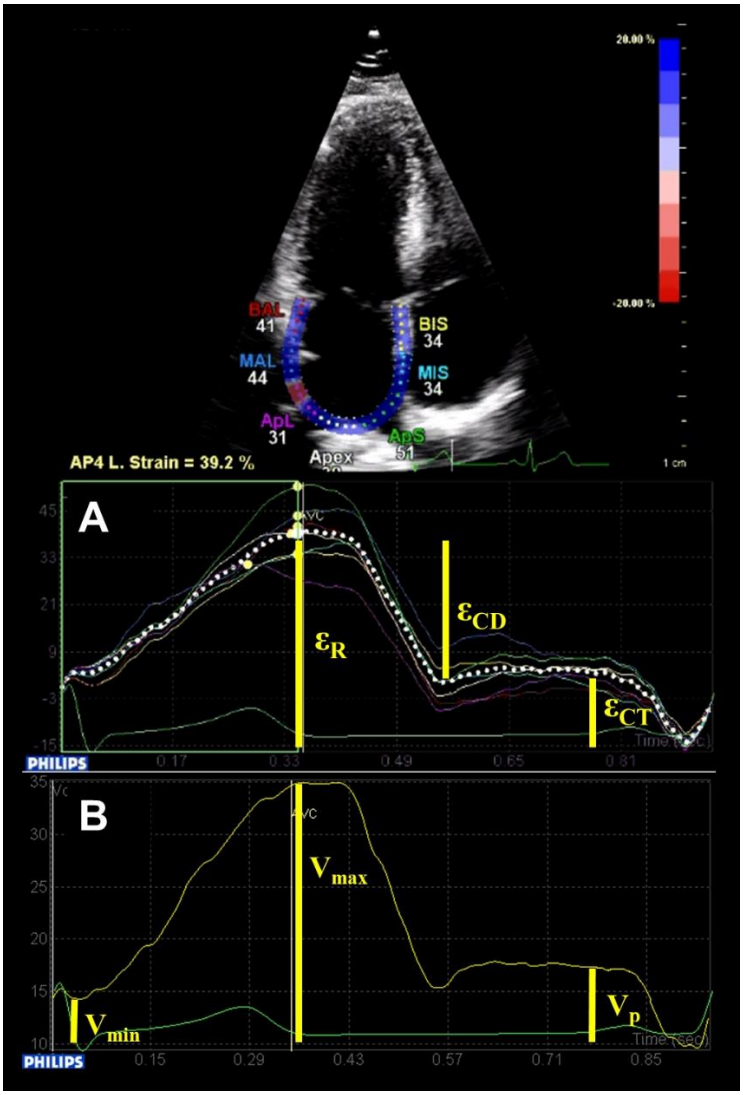

Figure 2. Four-chamber view image depicting the analysis of LA strain using speckle tracking technique. The region of interest is optimized manually, and then LA strain curve is created by the speckle tracking software (A). Using the atrial borders created for speckle tracking analysis, LA volume curves are generated by the same software (B)

(ε_R: reservoir strain; ε_{CD}: conduit strain; ε_{CT}: contractile strain; V_{max}: maximal volume; V_{min}: minimal volume; V_p: volume at the beginning of P wave)

5.5. 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 **(Figure 2B)**. 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) was calculated as $([V_{max} - V_{min}]/V_{max}) \times 100$. Expansion index (EI) was calculated as $([V_{max} - V_{min}]/V_{min}) \times 100$. Active emptying fraction (AEF) was calculated as $([V_p - V_{min}]/V_p) \times 100$. Passive emptying fraction (PEF) was calculated as $([V_{max} - V_p]/V_{max}) \times 100$ **(Table 1)**. TEF and EI have been assumed to reflect LA reservoir function and AEF and PEF to reflect LA contractile and conduit function, respectively.[69]

5.6. NT-proBNP measurements

Blood samples were obtained immediately prior to the echocardiographic studies. Plasma concentrations of NT-proBNP were analysed by electrochemiluminescence immunoassay (Elecsys 2010 system, Roche Diagnostics, Mannheim, Germany). NT-proBNP value > 220 pg/ml was defined as the evidence of the elevated LV filling pressure.[49]

5.7. Statistical analysis

Categorical data were expressed as frequencies and percentages; continuous data were expressed as the mean $\pm$ SD.

Comparisons of data between two groups were performed using independent-sample t-tests or independent Mann–Whitney test for continuous variables and chi square tests for categorical variables. Comparisons of data between more groups were performed with the use of multivariate analysis of variance (MANOVA) with Tukey post hoc test. In addition to the F value and the p value, the most used Wilks Λ is also reported, which is a measure of the percentage variance in dependent variables not explained by the independent variable.

Since concentration of NT-proBNP did not show normal distribution, logarithmic transformation was performed. 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. Sensitivity and specificity were computed for LA stiffness using various possible cut-off points.

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. Intraobserver and interobserver variability was assessed by the intraclass correlation coefficient. A p value of < 0.05 was considered significant. Data were analysed using IBM SPSS 22 statistical software.

6. RESULTS

From the total cohort of 80 patients, 72 were eligible for the study. Eight subjects were excluded from analysis due to LA foreshortening (3), or inadequate acoustic window (5). The average frame rate was 89 frames/sec.

Intraclass correlation coefficients for intraobserver variability were 0.982, 0.945, 0.908, 0.944, 0.903, and 0.913 for ε_R, ε_{CD}, ε_{CT} and V_{max}, V_p, V_{min}, respectively. Regarding interobserver variability, intraclass correlation coefficients for ε_R, ε_{CD}, ε_{CT} and V_{max}, V_p, V_{min} were 0.974, 0.932, 0.898, 0.931, 0.899 and 0.882, respectively.

6.1. 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 2.**

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 (≥ 55%) in 70 (97%), while mildly reduced (45–54%) in 2 (3%) patients. On the other hand, LV GLS was significantly reduced while LVM index was significantly higher in SSc patients. The grade of the mitral regurgitation and 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.

V_{max} index values were similar in the two groups, while V_{min} index and 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 3.**

Table 2. 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**
Diffuse cutaneous SSc (%)		39 (54)	
Duration of the disease (years)		7.3 ± 5.9	
Comorbidities			
Systemic arterial hypertension n (%)		40 (56)	
Medication			
ACE inhibitors n (%)		34 (47)	
Beta-blockers n (%)		24 (33)	
Calcium-channel blockers n (%)		36 (50)	
Loop diuretics n (%)		32 (44)	
Aldosterone receptor antagonists n (%)		18 (25)	
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**
LVM index (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)	

Statistically significant p-values are formatted in bold ($p < 0.05$).
BSA: body surface area; SSc: systemic sclerosis; ACE: angiotensin-convertase-enzyme; LV: left ventricular; EF: ejection fraction; LVM: left ventricular mass; PASP: systolic pulmonary artery pressure

Table 3. 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**

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

6.2. 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. There was a statistically significant difference between the groups on the combined dependent variables, $F(48.217) = 6.226$, $p < 0.0005$; Wilks' $\Lambda = 0.077$; partial $\eta^2 = 0.575$ using MANOVA with Tukey's post hoc test.

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 (**Table 4).**

Table 4. Clinical and echocardiographic parameters in healthy persons and in the SSc subgroups with different LV diastolic function

	Healthy volunteers (n=30)	SSc patients (n=72)			p
		Normal relaxation (n= 24)	Impaired relaxation (n= 23)	Pseudonormal (n= 25)	
Age (y)	55.2 ± 6.7 °° ˣˣ ##	45.4 ± 9.6 ˣˣ ##	62.7 ± 6.4	63.1 ± 6.7	**<0.001**
Duration of the disease (y)		4.3 ± 4.9 ##	6.7 ± 4.7 #	10.7 ± 6.3	**<0.001**
NT-proBNP (pg/ml)		93.4 ± 48.1 ##	130.9 ± 103.2 ##	304.8 ± 180.9	**<0.001**
LV EF (%)	63.3 ± 2.5 #	61.7 ± 3.8	60.8 ± 4.0	60.1 ± 5.6	**0.039**
LV GLS (%)	-19.3 ± 1.5 ˣˣ ##	-18.0 ± 2.4	-16.9 ± 2.0	-16.6 ± 2.4	**<0.001**
LVM index (g/m^2)	83.3 ± 11.6 ˣˣ ##	84.7 ± 15.4 ˣˣ ##	101.7 ± 19.6	104.3 ± 17.9	**<0.001**
Averaged mitral annular e' (cm/s)	10.9 ± 1.4 ˣˣ ##	10.4 ± 1.5 ˣˣ ##	7.3 ± 1.5	7.1 ± 1.3	**<0.001**
Mitral E/e'	7.4 ± 1.4 ˣ ##	7.4 ± 1.9 ˣ ##	8.9 ± 1.6 #	11.6 ± 2.9	**<0.001**
V_{max} index (ml/m^2)	24.3 ± 5.7 ##	22.2 ± 6.4 ##	22.3 ± 5.6 ##	30.2 ± 8.1	**<0.001**
V_{min} index (ml/m^2)	9.2 ± 3.0 ##	9.6 ± 3.4 ##	10.1 ± 3.2 ##	15.3 ± 6.4	**<0.001**
V_p index (ml/m^2)	13.4 ± 3.7 ##	13.3 ± 4.9 ##	14.4 ± 4.4 ##	20.6 ± 7.5	**<0.001**
TEF (%)	62.6 ± 5.0 ° ˣˣ ##	56.7 ± 7.6	54.4 ± 8.1	50.8 ± 10.0	**<0.001**
EI (%)	171.9 ± 37.0 ° ˣˣ ##	137.5 ± 38.5	126.5 ± 41.9	112.7 ± 48.8	**<0.001**
PEF (%)	44.9 ± 6.8 ˣˣ ##	40.9 ± 9.1 #	35.7 ± 8.9	33.1 ± 9.9	**<0.001**
AEF (%)	31.4 ± 9.1	26.5 ± 9.3	28.7 ± 11.0	26.9 ± 7.7	0.188
ε_R (%)	51.8 ± 7.4 °° ˣˣ ##	45.1 ± 8.1 ##	42.2 ± 6.6 #	36.6 ± 7.3	**<0.001**
ε_{CD} (%)	27.1 ± 4.6 ˣˣ ##	26.9 ± 5.7 ˣ ##	20.6 ± 6.1	19.5 ± 5.3	**<0.001**
ε_{CT} (%)	24.8 ± 4.9 °° ˣ ##	18.2 ± 4.4 ˣ	21.5 ± 2.8 ##	16.8 ± 3.6	**<0.001**

Statistically significant p-values are formatted in bold ($p < 0.05$). Abbreviations as in Tables 2 and 3.

° p<0.05 versus SSc patients with normal relaxation
°° p<0.01 versus SSc patients with normal relaxation
ˣ p<0.05 versus SSc patients with impaired relaxation
ˣˣ p<0.01 versus SSc patients with impaired relaxation
# p<0.05 versus SSc patients with pseudonormal pattern
p<0.01 versus SSc patients with pseudonormal pattern

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, LVM index was significantly higher in patients with LV diastolic dysfunction.

ε_R values were significantly lower in all SSc subgroups than those in healthy subjects. No significant difference was found between ε_R values of patients with normal and impaired relaxation. On the contrary, ε_{CD} was preserved in SSc patients with normal LV relaxation while reduced in both groups with LV diastolic dysfunction. ε_{CT} values were significantly lower in all SSc subgroups than those in healthy subjects. Nevertheless, significantly higher ε_{CT} values were measured in the impaired relaxation subgroup compared with the other two SSc subgroups (**Figure 3A**).

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 ε_R and ε_{CD}, 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 3B**).

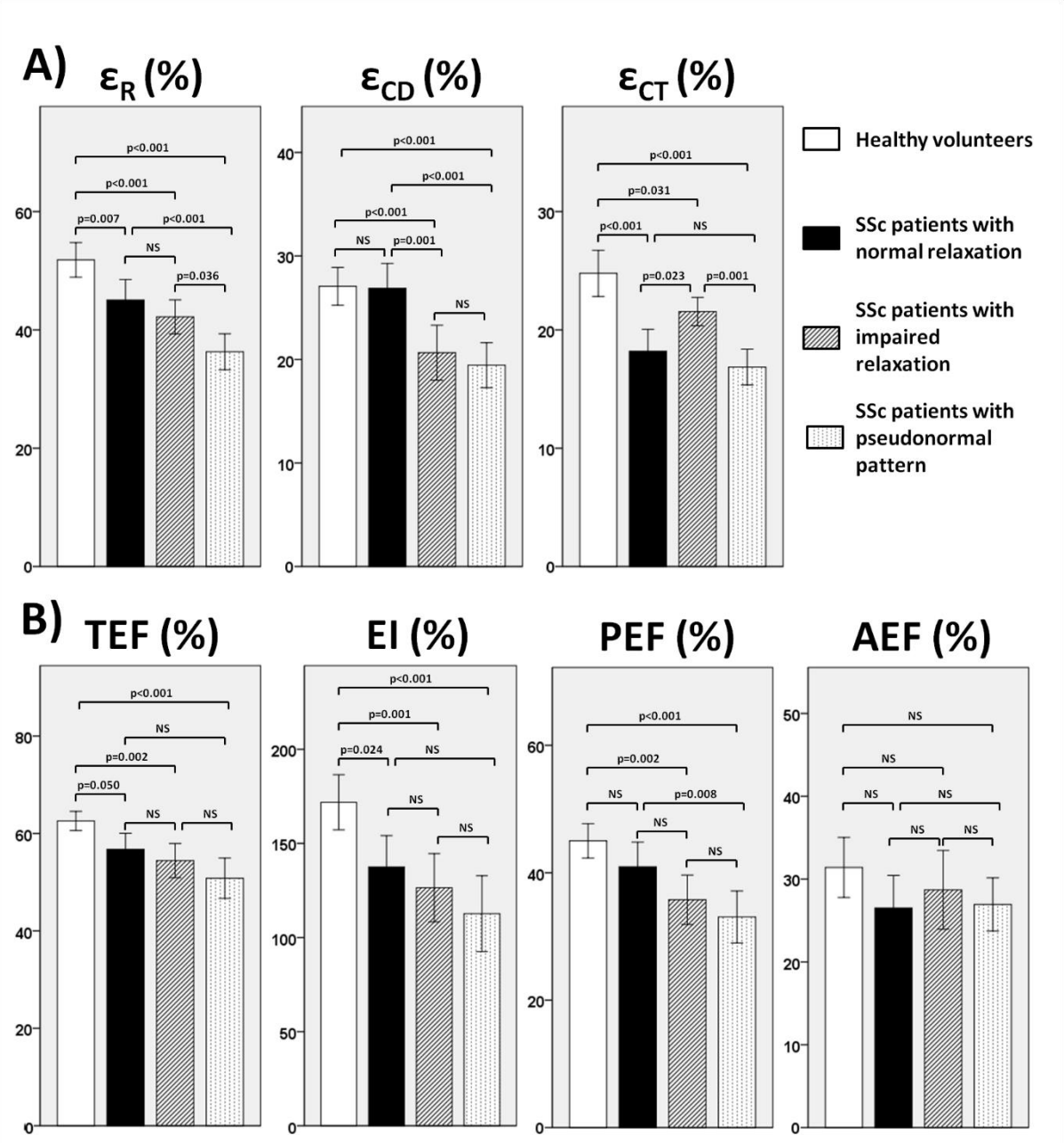

Figure 3. Progression of strain (A) and phasic volume indices (B) parallel with the worsening of the LV diastolic function in SSc patients and comparison with the parameters of healthy subjects

(ε_R: reservoir strain; ε_{CD}: conduit strain; ε_{CT}: contractile strain; TEF: total emptying fraction; EI: expansion index; AEF: active emptying fraction; PEF: passive emptying fraction)

6.3. 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 5**.
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 ε_R 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.

Univariate and multivariate predictors of the NT-proBNP level are reported in **Table 6**. 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.

Table 5. 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 (%)	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**
LVM index (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**

Statistically significant p-values are formatted in bold ($p < 0.05$). Abbreviations as in Tables 2 and 3.

Table 6. Predictors of the (ln) NT-proBNP in univariate and multivariate regression analyses

	Univariate analysis		Multivariate analysis	
	r	**p**	**β**	**p**
Age (y)	0.384	**0.001**		
BSA (m^2)	-0.160	0.178		
Duration of the disease (y)	0.233	**0.049**		
eGFR (ml/min/1.73m^2)	-0.502	**<0.001**	-0.409	**<0.001**
LV EF (%)	-0.209	0.079	-0.194	**0.048**
LA V_{max} index (ml/m^2)	0.285	**0.015**		
LA ε_R (%)	-0.238	**0.044**		
LA stiffness	0.431	**<0.001**	0.287	**0.007**

Statistically significant p-values are formatted in bold ($p < 0.05$). Abbreviations as in Tables 2 and 3.

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 4**.

Sensitivity and specificity values were computed for LA stiffness using various possible cut-off points (**Figure 5**). 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%.

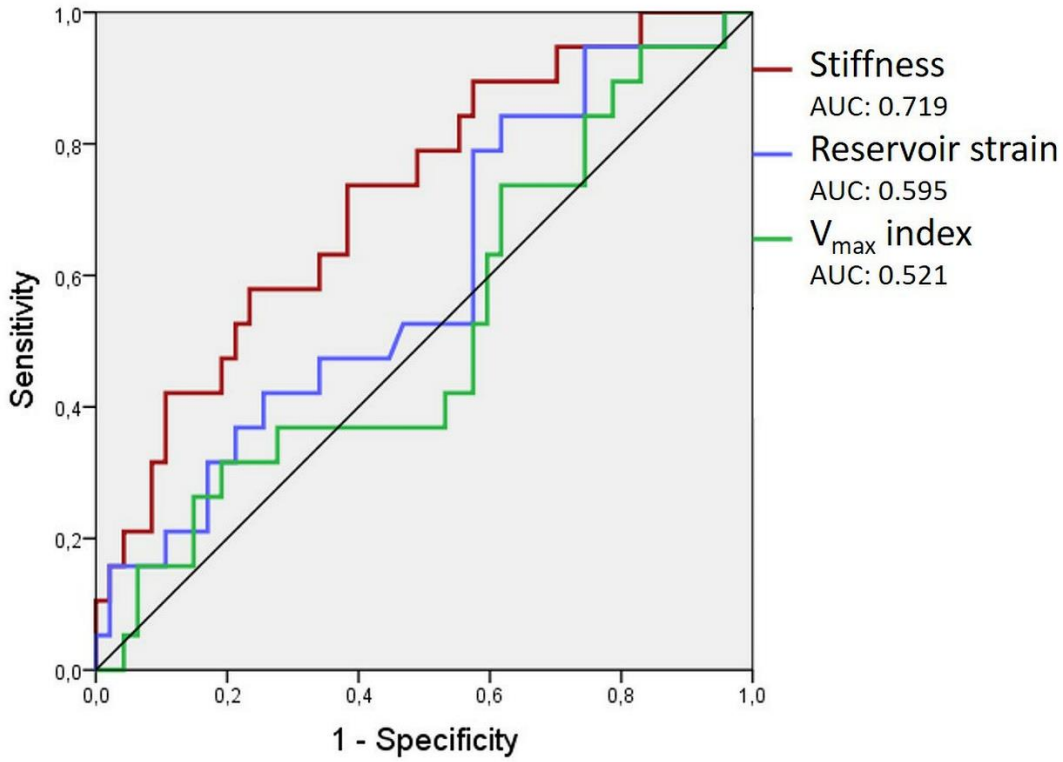

Figure 4. ROC curves for maximal LA volume index, LA reservoir strain and LA stiffness for the prediction of NT-proBNP > 220 pg/ml

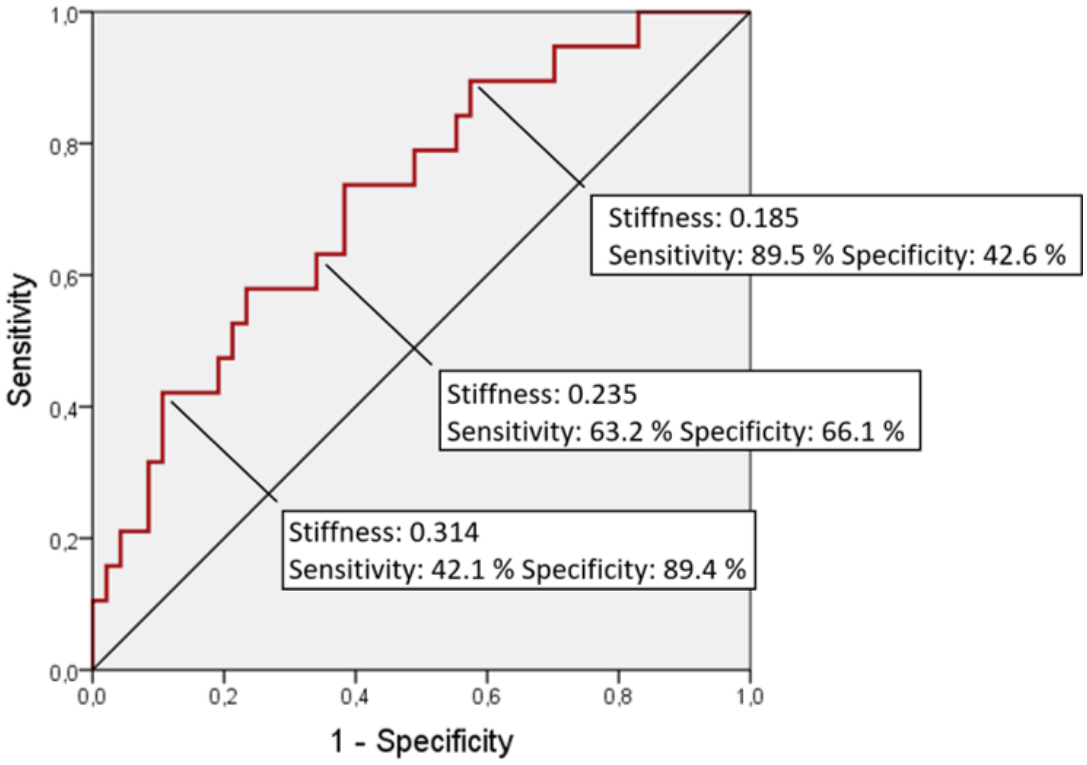

Figure 5. ROC curve displaying the sensitivity and specificity of various LA stiffness values in predicting NT-proBNP > 220 pg/ml

7. DISCUSSION

The prevalence of HFpEF has increased over the last 2 decades. In addition, its incidence is expected to continue to rise in association with the aging population and the increasing prevalence of risk factors such as hypertension, obesity, and diabetes mellitus.[34] Although HFpEF is a growing clinical and public health problem, many crucial aspects of the syndrome still remain unclear, including pathophysiology, early diagnosis and treatment.

Echocardiography has a pivotal role in diagnosis of LV diastolic dysfunction which is considered as the hallmark pathophysiological process in HFpEF. Despite several guidelines and recommendations on diagnosis of impaired LV diastolic function and elevated LV filling pressure, the early and reliable detection is still challenging in the everyday practice. The conventional echocardiographic parameters have several limitations and are often inconclusive, therefore there is a continuing search for new, additional non-invasive parameters. Over the past two decades, growing evidence supports the importance of the LA structure and function in HF. Primarily the LA volume was reported as a sensitive indicator of the severity and duration of elevated LV filing pressure and as a predictor of adverse cardiovascular outcomes in HF thus its use is suggested in the current guidelines.[6,60,80,84,85] Nowadays more attention is devoted to the LA function, which may serve as an even more powerful diagnostic and prognostic marker in HF.[16,17]

In SSc, LV diastolic dysfunction and the consequential HFpEF are reported to be frequent as they reflect the primary myocardial involvement of the disease.[3–5] 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.

7.1. Left atrial size and function in systemic sclerosis: comparison with healthy subjects

In HFpEF patients the structural and functional remodelling of the LA has been reported as an early and reliable indicator of LV diastolic dysfunction and elevated LV filling pressure.[16,17,80] In SSc, however, few data are available about LA size and function.

Ágoston et al., with the use of 2D STE-derived strain measurements, found reduced LA reservoir and conduit function in SSc patients compared with healthy subjects, whereas LA

contractile function was preserved in their SSc population. LA V_{max} index values were similar to those in healthy subjects.[105] On the other hand, Ataş et al. reported higher LA volume values in SSc patients compared with a healthy control population, and all phasic volume indices suggested impaired LA function.[106]

Our results are partially in line with previous findings: although LA V_{max} index values were similar in our SSc patients and in the healthy group, we found significantly enlarged V_{min} and V_p indices in the SSc group. Consequently, all phasic volume indices except AEF were significantly reduced in the SSc group. In addition, all LA strain parameters were lower than those in healthy subjects.

7.2. Worsening of left atrial parameters parallel with the decline of the left ventricular diastolic function

Mainly based on tissue Doppler measurements, recent studies suggested that LV diastolic dysfunction is prevalent in SSc.[2–4] In previous longitudinal studies, a clear association has been reported between disease duration and the severity of LV diastolic dysfunction in SSc.[3,4] In the present work, we confirmed the significant prevalence of LV diastolic dysfunction in our SSc population and investigated the LA size and the phases of the LA mechanics in the different stages of LV diastolic (dys)function.

Ataş et al. reported higher LA volume values and impaired LA phasic function in SSc patients compared with healthy controls. Nevertheless, they could not find differences in either volumetric parameters or phasic volume indices in patients with and without LV diastolic dysfunction. In their SSc population both lateral and septal e' values were in the normal range, suggesting that the majority of their patients were in the early phase of the disease.[106] Still, because in patients without the presence of significant mitral valve disease or history of atrial fibrillation, LA size serves as a reliable indicator of the severity and time duration of the elevated filling pressure, the results of Ataş et al. seem to be contradictory. In contrast to the data of Ataş et al., 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)[6], but because the high specificity and low sensitivity of this cut-off value is well known[87], 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.[17,67,107–109] In addition, this phenomenon may explain why LA contractile function was preserved in the SSc population investigated by Ágoston et al.[105]

LA V_{max} index is mentioned in the recent guideline as a useful marker for identification of LV diastolic dysfunction.[6] 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. Similar conclusions were reported by Singh at al. for a general population with preserved LV EF. In their study, ε_R showed significant decrease parallel with the worsening of the LV diastolic dysfunction, allowing accurate categorization of the patients, whereas LA V_{max} index was not useful for this purpose because significant overlap was found between V_{max} index values measured in the different subgroups.[17] In addition, in a large multicenter study, Morris at al found that ε_R was able to detect subtle LA dysfunction in patients with LV diastolic dysfunction even though LA volumes were normal.[16] Clear similarities may be found between our data and the results of those two studies. Nevertheless, our data suggest that parameters of the LA mechanics are even more sensitive in the detection of myocardial involvement than the tissue Doppler parameters conventionally used for the diagnosis of LV diastolic dysfunction. Our results are in line with the findings of Cameli et al., who reported compromised ε_R in asymptomatic untreated hypertensive patients with preserved LV EF and normal LV diastolic function, despite normal LA cavity size, suggesting preclinical LA myocardial dysfunction.[95]

This analogy suggests that our data are not disease specific but may be generally found in LV diastolic dysfunction. In this very early phase of the disease, the rise in LV filling pressure may be transient and/or subclinical and unnoticed with the use of conventional Doppler and tissue Doppler echocardiographic techniques. Our data suggest, however, that ε_R is useful for the detection of this early impairment. Similarly, ε_{CT} is a suitable tool when the aim is to detect enhanced contractile function of the LA in the early phase of LV diastolic dysfunction. On the other hand, phasic volume indices of the LA mechanics seem not to be sensitive enough for these purposes.

Reduced LV GLS is suggested in the current guideline as an additional parameter for the evaluation of LV diastolic function when the conventional data are inconclusive. Its value was already significantly reduced in our SSc patients with normal relaxation compared with the healthy subjects and showed further decline in patients with pseudonormal pattern. Unlike ε_R, however, significant overlap was found between GLS values in patients with impaired relaxation and pseudonormal pattern. Thus, LV GLS also may be useful in the early detection of primary myocardial involvement in SSc, but it does not show a continuous significant decline parallel with the worsening of LV diastolic function.

7.3. Comparison of the diagnostic power of left atrial parameters in predicting elevated left ventricular filling pressure

The diagnostic hallmark of HF is elevated LV filling pressure, a compensatory response to sustain cardiac output. Thus, assessment of LV filling pressure has important diagnostic and prognostic implications in SSc. Although cardiac catheterization remains the gold standard, echocardiography is usually the first test to perform. Thus, there is a continuing search for non-invasive markers of elevated LV filling pressure. The previously used parameters have several limitations and reflect different physiological aspects of the diastole. E/e′ - the ratio of the early diastolic velocity of the mitral inflow to early diastolic velocity of the mitral annulus - 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.[7,51–54] Particularly weak correlations were observed in the so called grey zone (average E/ e′ between 10 and 14[6]; septal E/e′ between 8 and 15[40]; lateral E/e′ between 8 and 12[55]). Thus, additional echocardiographic parameters are also required for identifying elevated LV filling pressure.

LA V_{max} index has been reported as a useful biomarker of the severity and duration of the elevated LV filling pressure, especially in patients without significant valvular heart disease or history of atrial fibrillation[80]. Thus the current recommendation of ASE/EACVI suggests the use of LA V_{max} index as additional parameter for the evaluation of LV filling pressure.[6]

Recent studies proved, however, that the enlargement of the cavity is preceded by the functional remodelling of the LA.[17,91] 2D STE-derived LA ε_R showed significant correlation with the amount of LA wall fibrosis as assessed by cardiac MRI as well as with LA interstitial fibrosis in patients with mitral valve disease in histopathologic specimens.[110,111] This parameter showed a good correlation with the invasively measured LV filling pressure, exceeding the diagnostic power of the LA V_{max} index.[10,12,17,97,112]

Beside LA ε_R, 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.[18,19] Kurt et al. reported LA stiffness as a useful index to differentiate between HFpEF and asymptomatic diastolic dysfunction.[19] In the study of Pilichowska-Paszkiet et al. LA fibrosis was detected by electroanatomical mapping in patients with atrial fibrillation. LA stiffness showed more robust correlation with the extent of LA fibrosis compared with LA strain.[113]

Thus we aimed to compare the diagnostic power of LA V_{max} index, LA ε_R 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. The diagnostic power of NT-proBNP in this context was previously proved: In the study of Tschöpe et al. NT-proBNP showed stronger correlation with the invasively measured LV filling pressures than the conventional echocardiographic parameters.[114] In addition, NT-pro BNP is also known as a strong predictor of outcome in HFpEF patients[115], and in previous studies showed strong independent correlations with the LA volume and LA ε_R values in HFpEF.[86,97] NT-proBNP > 220 pg/ ml is considered to have a high positive predictive value for the diagnosis of HFpEF[49,88], 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 ε_R. 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.[6,87] 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.

7.4. Limitations

Numerous limitations of our study need to be acknowledged. For obtaining LA strain values, we used a software that was developed for LV strain analysis because a dedicated software for atrial strain estimation was not available.

Although our data suggest that there is a continuous significant decline in LA function parallel with the worsening of LV diastolic dysfunction in SSc, we could not prove that this worsening continues in the most severe form of diastolic dysfunction, because no patients with restrictive mitral inflow pattern participated in the study.

The confounding effect of other variables, such as age and comorbidities, on LA volume and function was not investigated in our studies.

The major limitation of our studies is the lack of invasive measurements: LV filling pressure was estimated non-invasively, based on NT-proBNP levels. Nevertheless, the key role of this biomarker in predicting elevated LV filling pressures has been repeatedly confirmed in the current recommendation.[88] Besides, larger sample size and prospective follow-up are needed to assess the prognostic impact of the impaired LA mechanics and elevated LA stiffness in SSc population.

8. 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.

9. 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.

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