







# Comparative study of left ventricular function in a group of asymptomatic patients with systemic sclerosis and a control group

Badanie porównawcze czynności lewej komory w grupie chorych  
z bezobjawową twardziną układową i w grupie kontrolnej

Meriem Drissa , Amine Boussema , Marouene Haloui ,  
Mohamed Amine Soula , Marwa Chebbi , Habiba Drissa 

Service de Cardiologie Adultes, Hôpital La Rabta, Tunis, Tunisia

## Abstract

**Introduction.** Cardiac involvement in systemic sclerosis (SSc) represents a major cause of morbidity and mortality and constitutes a turning point in this disease.

The aim of this study was to describe echocardiographic data in asymptomatic patients with SSc and compare them to results obtained in a control population in order to unmask subclinical cardiac involvement during systemic sclerosis.

**Material and methods.** A prospective study was conducted between 2012 and 2017 including two groups: group A included 25 asymptomatic scleroderma patients without other comorbidities, while group B consisted of 25 control and healthy subjects. The two groups were examined by echocardiography coupled with tissue Doppler and 2D strain.

**Results.** The mean age of our patients was  $45 \pm 7$  years. The sex ratio was 0.8. The control population was epidemiologically similar to the group of patients. The anatomical data of the left ventricle and the ejection fraction were normal and comparable between the two groups, but the Tei index was significantly higher in group A ( $0.8 \pm 0.04$  vs.  $0.28 \pm 0.07$ ,  $p < 0.01$ ). Tissue Doppler velocity S peak measurement was reduced in group A compared to group B ( $5.6 \pm 0.5$  vs.  $9.30 \pm 0.5$ ,  $p < 0.01$ ), and global longitudinal strain was also altered in scleroderma patients ( $-11 \pm 0.4$  vs.  $-18 \pm 0.3$ ,  $p < 0.01$ ). There was no significant difference in E/A ratio, however early left ventricular diastolic dysfunction was revealed by a higher E/Ea and E/Vp ratio in group A compared to group B with respectively ( $13 \pm 1.8$  vs.  $6 \pm 1.6$ ,  $p < 0.01$ ) and ( $2.2 \pm 0.6$  vs.  $1.5 \pm 0.6$ ,  $p < 0.01$ ), a longer Ap–Am duration ( $\geq 20$  ms), and a higher volume of the left atrium was noted in group A. The mean value of the pulmonary pressures was  $37.9 \pm 9$  mm Hg in patients with scleroderma versus  $25 \pm 3$  mm Hg for the control group ( $p < 0.01$ ). There was no right ventricular dysfunction.

**Conclusions.** Cardiac involvement during systemic sclerosis precedes clinical expression. Echocardiography coupled with tissue Doppler and 2D strain are useful to detect these abnormalities at a subclinical stage of the disease.

Key words: systemic sclerosis, cardiac involvement, echocardiography, comparison

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## Introduction

The occurrence of cardiac involvement in systemic sclerosis (SSc) is an evolutionary turning point in this disease

and represents a major cause of morbidity and mortality from this systemic pathology. It appears that histological lesions of the heart in SSc would be much more frequent and earlier than clinical symptoms.

Address for correspondence: Meriem Drissa MD, Service de Cardiologie Adultes, Hôpital La Rabta, Tunis, Tunisia, e-mail: drissameriem@yahoo.fr

The aim of this study was to unmask any signs of left ventricular dysfunction in a subclinical stage of the disease of scleroderma by appreciating echocardiography systolic and diastolic function in asymptomatic patients with SSc, and to compare the echocardiographic findings in these patients to those with the results obtained in a control population.

## Material and methods

A prospective descriptive and comparative study was conducted in the adult cardiology department of the Rabta Hospital from 2012 to 2017. This relatively long inclusion period was due to the difficulty of recruiting patients because of the rarity of this systemic disease, to which is added the imperative that these patients must be functionally asymptomatic and free from any other comorbidity.

### Inclusion criteria:

- group A: 25 asymptomatic scleroderma patients without signs of heart failure who did not have other comorbidities that could interfere with left ventricular function;
- group B: 25 control and healthy subjects.

**Exclusion criteria** – patients with high blood pressure, diabetes, valvular heart disease, ischaemic heart disease.

Patients were examined using conventional echocardiography coupled with tissue Doppler and two-dimensional (2D) strain. Several parameters were collected and compared between the two groups, in particular: left

ventricular anatomic measurements (diameter, septum thickness), left ventricular function [ejection fraction (EF), Tei index, S wave at tissue Doppler, as well as global longitudinal strain] and diastolic function (mitral profile, E/E wave ratio, Vp, duration of the mitral wave minus the pulmonary wave, left atrium volume).

## Statistical studies

We calculated simple frequencies and relative frequencies (percentages) for qualitative variables, means, medians and standard deviations (standard deviations) for quantitative variables. We used the chi-square test and the student test respectively for the comparison of two percentages and two averages. In all the statistical tests, the significance level was fixed at 0.05.

## Results

Epidemiological data of the two groups are set out in Table 1.

Both groups A and B were free from comorbidities (e.g. arterial hypertension, diabetes, ischaemic heart disease). The diagnosis of SSc in our patients went back several years, with an average of 6.5 years. All our patients were treated with corticosteroids; 55% of patients received calcium channel blockers due to Raynaud’s syndrome.

Anatomical features and left ventricular systolic function for both groups are set out in Table 2.

**Table 1.** Epidemiological characteristics of study population

Variable	Group A	Group B	p
Age, years	45 ± 7	43 ± 7	NS
Sex ratio (female)	0.8	0.8	NS
Body mass index [kg/m <sup>2</sup> ]	22 ± 1	24 ± 4	NS
Diabetes	5.6 ± 0.8	5.3 ± 0.6	NS
Systolic BP [mm Hg]	121 ± 1	117 ± 2	NS
Diastolic BP [mm Hg]	78 ± 5	72 ± 5	NS

BP – blood pressure; NS – not significant

**Table 2.** Anatomical features and left ventricular systolic function in both groups

Variable	Group A (25 patients)	Group B (25 patients)	p
LVEDd [cm]	47 ± 0.5	45 ± 0.5	0.1
SIV [cm]	0.9 ± 0.1	0.8 ± 0.1	0.2
PP [cm]	0.9 ± 0.15	0.8 ± 0.1	0.6
EF [%]	63 ± 3	64 ± 1	0.45
Tei index	0.6 ± 0.08	0.28 ± 0.07	< 0.01
Peak S velocity [cm/s]	5.6 ± 0.5	9.3 ± 0.5	< 0.01
GLS [%]	-11 ± 0.4	-18 ± 0.3	< 0.01

LVEDd – left ventricular end-diastolic diameter; IVS – interventricular septum; LVPW – left ventricular posterior wall; EF – ejection fraction; GLS – global longitudinal strain

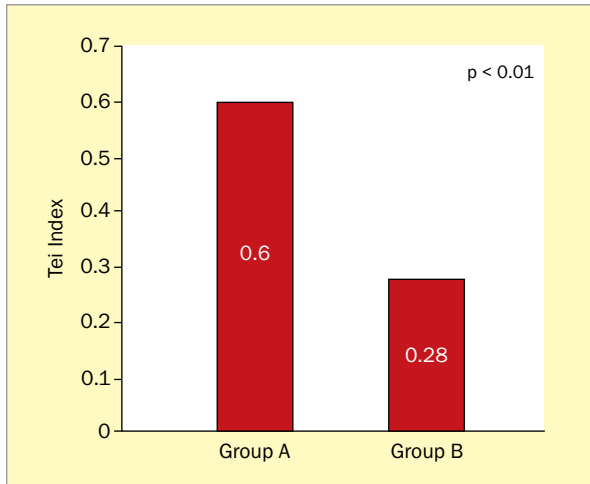


Figure 1. Comparison of Tei index between groups

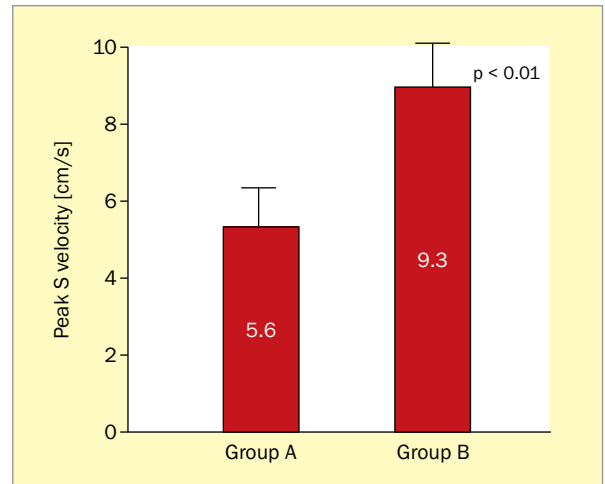


Figure 2. Comparison of peak S velocity between groups

Left ventricular diameter measurements and septum thickness were normal and comparable between the groups. The Tei index in the group of scleroderma patients was  $0.6 \pm 0.08$ . This was significantly higher than in the control group which was  $0.28 \pm 0.07$  (Figure 1). This suggests the existence of an attributable left ventricular dysfunction during SSc that will have to be apprehended by other ultrasound methods.

The left ventricular ejection fraction was also comparable between the groups. The peak of systolic velocities S at the mitral annulus measured by the tissue Doppler mode (DTI) and the global longitudinal strain was definitely lowered in group A compared to group B, attesting to latent left ventricular systolic dysfunction in our scleroderma patients in the subclinical stage (Figures 2, 3).

The study of the diastolic function of the left ventricle is set out in Table 3. The analysis of the parameters of the diastolic function by the pulsed Doppler mode shows no significant differences between the groups with respect to velocity peaks, protodiastolic E, end-diastolic A, or E/A ratio. A normal or pseudo-normal filling pattern was found in 82% of patients in group A and in 93% of group B.

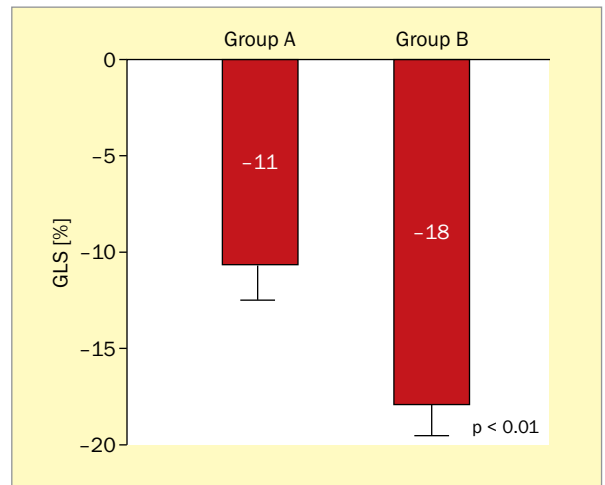


Figure 3. Comparison of global longitudinal strain (GLS) between groups

A significant difference between the groups was found concerning combined indices (E/Vp, E/Ea ratio, and left atrial volume; Figures 4–7).

Table 3. Features of diastolic left ventricular function

Variable	Group A	Group B	p
Peak E velocity [cm/s]	89 ± 14	87 ± 16	0.6
Peak A velocity [cm/s]	65 ± 12	64 ± 16	0.4
E/A ratio	1.46 ± 0.3	1.32 ± 0.4	0.3
E/Vp ratio	2.3 ± 0.6	1.3 ± 0.6	< 0.01
Am–Ap duration [ms]	0	> 20	< 0.01
Peak velocity at mitral annulus Ea [cm/s] TD	7.0 ± 1.2	11. ± 1.4	< 0.01
E/Ea ratio	12.71 ± 1.8	7.9 ± 1.4	< 0.01
Volume of left atrium [mL/m <sup>2</sup> ]	37.2 ± 9	25 ± 3	< 0.01

TD – tissue Doppler

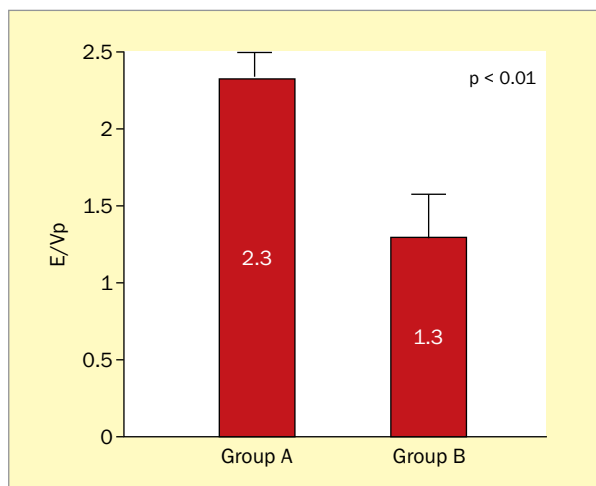


Figure 4. Comparison of E/Vp between groups

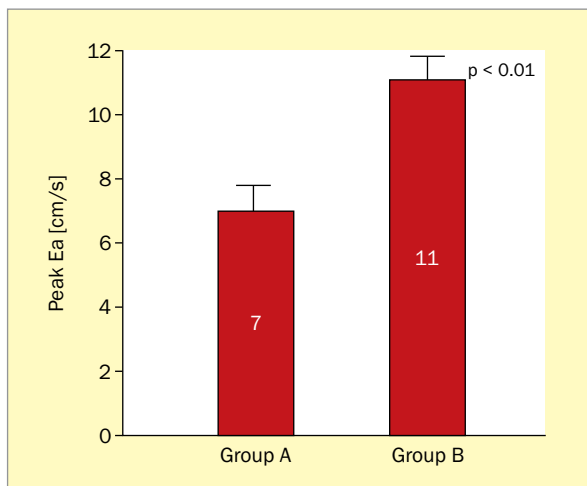


Figure 5. Comparison of Ea between groups

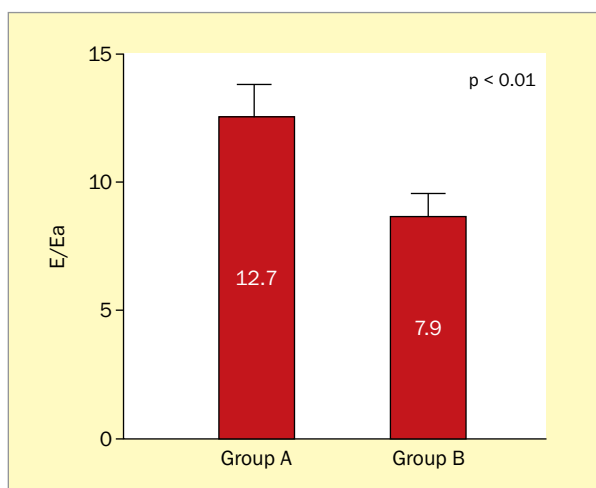


Figure 6. Comparison of E/Ea between groups

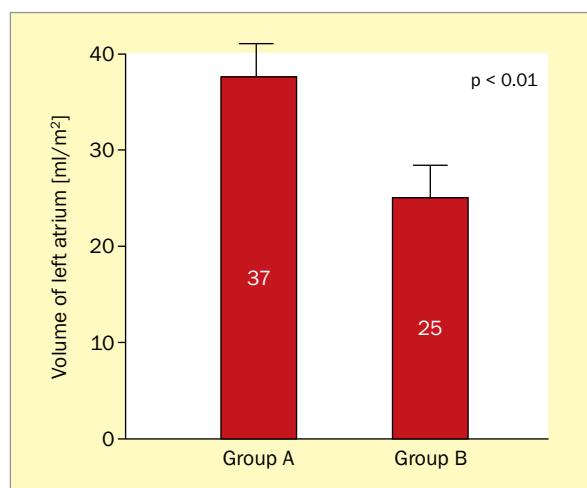


Figure 7. Comparison of volume of left atrium between groups

The elevation of pulmonary arterial pressures is one of the echocardiographic abnormalities found in our scleroderma patients. The mean value pulmonary pressures were  $37 \pm 9$  mm Hg for group A versus  $25 \pm 3$  mm Hg for group B ( $p < 0.01$ ). However, this relative pulmonary hypertension was not important, explaining the absence of functional impairment especially in our scleroderma patients. Moreover, there was no dysfunction of the right ventricle in both groups.

## Discussion

Systemic sclerosis is a generalised disease of interstitial and vascular connective tissue associated with abnormalities of the immune system (autoimmune disease) leading to fibrosis. The disease usually begins between the ages

of 40 and 60 [1]. The average age of our patients was  $45 \pm 7$  years. Women are more frequently affected than men (sex ratio 8/10) [1], and this predominance was found in our study. Cardiac involvement in SSc is multiple and not very specific [2]. Lesion of pericardium and valves may occur but myocardial involvement is preponderant. This seems to be due to the combination of several mechanisms: myocardial ischaemia in relation to coronary vasospasm, myocardial fibrosis, and obliteration of the coronary microcirculation or an alteration of the capillary bed, all contributing to myocardial dysfunction [3].

Cardiac involvement is usually asymptomatic, which is why its prevalence is underestimated: 8–28% depending on the studies [4]. Postmortem studies have reported myocardial involvement in 50–89% of subjects with SSc [5]. Indeed Angelo [5], in his autopsy series including

58 patients, showed myocardial fibrosis in 81% of patients, while only 16% had cardiac manifestations during their lifetime. Histological and echocardiographic cardiac involvement precedes clinical expression, hence the interest in performing echocardiography in subjects with scleroderma to detect abnormalities of systolic and diastolic function that may appear several years before causing clinical signs [6]. Several studies [7, 8] have not noted a change in the anatomical features of the left ventricle (LV) during scleroderma. In our series, the values of anatomical parameters of LV were normal and comparable between the groups.

Myocardial involvement in SSc affects more often diastolic than systolic function. Indeed several studies have demonstrated that scleroderma patients have a normal EF: the mean EF was 69.5% in the Candella study [9], 66.9% in the Meunes study [6], and 67.4% in the Plazak series [10]. In our series, the ejection fraction in patients with scleroderma was normal and comparable to the control group, with an average EF of 64%.

Tissue Doppler, by studying systolic velocities S at the mitral annulus, is more reliable than EF for the detection of early LV systolic dysfunction [11]. It therefore appears much more sensitive than conventional ultrasound [12]. This notion has been reported in several studies that have shown that despite a normal ejection fraction, there is a decrease in LV contractility in scleroderma patients detected by the study of tissue Doppler velocities. This attests to the existence of an early systolic dysfunction underestimated by echocardiography. In our series, although left ventricular ejection fraction (LVEF) was normal in patients with SSc, early systolic dysfunction was detected by a low value of the peak velocity of S measurement at the tissue Doppler.

Studies on the contribution of D2 strain in scleroderma patients are very rare. However, some authors have shown by an analysis of radial or longitudinal myocardial function its performance in the detection of systolic and early dysfunction of LV. This method was used by Coucelo [13], who studied the segments reflecting displacement of longitudinal fibres in scleroderma patients. He found a correlation between the deterioration of systolic and diastolic function in the studied segments and the degree of fibrosis. Edoardo Rosato similarly noted in his study of 76 scleroderma patients abnormalities in longitudinal fibres in 23% versus 8% in the function of radial fibres. In our series, GLS was altered in our scleroderma patients.

Myocardial involvement is much more often a diastolic lesion than a systolic one. This constitutes the essential manifestation of the primary cardiomyopathy of the SSc [4]. The transmural profile usually described in scleroderma patients is a type anomaly of relaxation. A mitral profile type I was found in 42% of sclerodermic patients in the study by Valentini [8]. A restrictive profile has also been reported

in the literature, but its frequency was lower; Fernandes [15] in a study with endomyocardial biopsies in asymptomatic patients without evidence of heart failure and excluding patients with hypertension, LV hypertrophy, and LV systolic dysfunction, found abnormality in the disposition of the patient collagen in 94%, indicating the almost constant myocardial involvement due to this fibrosis. Candell-Riera et al. [9] supports this view, noting in his study that diastolic dysfunction found in scleroderma patients persisted after adjustment for blood pressure, heart rate, age, valvulopathy, and pericardial effusion [16]. This confirms primary myocardial involvement in SSc.

In our study, the 25 patients were completely asymptomatic without any clinical signs of heart failure and were free from any comorbidity that could interfere with the function of LV. We did not notice anomalies in the mitral profile. It can be concluded that diastolic dysfunction is certainly common, but may simply be due to associated comorbidities and not to primary myocardial involvement. In addition, diastolic alteration specifically related to scleroderma can only be discussed once other possible causes of diastolic dysfunction have been ruled out.

All studies highlight the limitations of evaluating diastolic function on transmitral flow alone, hence the contribution of tissue pulsed Doppler as a non-invasive method in the study of diastolic function at a subclinical stage. Indeed, by the Ea peak measurement on the septal side of the mitral annulus to the tissue Doppler, Can [17] noted in patients with scleroderma a decrease in Ea compared to a control group, thus signalling early diastolic dysfunction. In our series, the tissue Doppler indicated a decrease in the value of Ea in scleroderma patients compared to the control group and confirmed eventual diastolic dysfunction. Another index of evaluating LV pressure was the E/Ea ratio. In fact, Can [17] calculated this ratio in a group of scleroderma patients and a healthy group. This ratio was higher in the group of patients, pointing to a rise in LV filling pressure. Our results are similar.

The duration of Ap-Am, E/Vp, and volume of the left atrium have not been the subject of many studies in the various series published in the literature. Most studies have been based on mitral flow analysis, velocity peak Ea measurement at the mitral annulus to tissue Doppler, and E/Ea ratio calculation. The values of these parameters were altered in our series, pointing to a rise in filling pressure.

The exact prevalence of pulmonary artery hypertension (PAH) during SSc has been debated, but is within the range of 8–12% [18]. According to the new classification proposed at the Third World Congress, pulmonary hypertension during SSc can be either a PAH associated with systemic sclerosis or pulmonary arterial hypertension secondary to pulmonary fibrosis [19]. PAH was observed in our patients but it was not important, which also explains the lack of functional impairment especially in our scleroderma patients.

Although diastolic dysfunction of the left ventricle, and to a lesser extent systolic dysfunction, has been well studied in scleroderma patients, right ventricular function has not been studied extensively [20].

### Limitations of the study

The small size of our population is the main limitation of our work. Further single or multi-centre studies including a larger number will improve the validity of our results.

We have not also developed the contribution of this echocardiographic study in the decision as to whether or not to prescribe treatment in a totally asymptomatic scleroderma patient.

### Conclusion

Our patients with scleroderma were completely asymptomatic and without any clinical signs of heart failure, but the comparative study with a healthy population has identified (by echocardiography coupled with tissue Doppler and 2D strain) the presence of a latent subclinical cardiac involvement in SSc. Diagnosis of its anomalies allows for an appropriate therapeutic approach (vasodilatory drugs) to early vasospastic and reversible abnormalities of early myocardial disease observed in scleroderma.

### Conflict(s) of interest

The authors declare no conflict of interest.

### Streszczenie

**Wstęp.** Zajęcie serca w twardzinie układowej (SSc) jest główną przyczyną chorobowości i śmiertelności oraz stanowi punkt zwrotny w przebiegu choroby.

Celem pracy jest opisanie obrazu echokardiografii u niewykazujących objawów chorych z SSc i porównanie z wynikami uzyskanymi w populacji kontrolnej, by wykryć subkliniczny proces chorobowego w sercu w przebiegu twardziny SSc.

**Material i metody.** Badanie prospektywne przeprowadzono w latach 2012–2017. Pacjentów podzielono na dwie grupy: grupa A składała się z 25 chorych z bezobjawową SSc bez chorób współistniejących, grupę B utworzono z 25 zdrowych osób stanowiących grupę kontrolną. W obu grupach przeprowadzono badania echokardiograficzne z dopplerowskim obrazowaniem tkanek i badaniem odkształcenia miokardium w obrazowaniu dwuwymiarowym (2D strain).

**Wyniki.** Średnia wieku pacjentów wynosiła  $45 \pm 7$  lat. Współczynnik płci wynosił 0,8. Grupa kontrolna była podobna pod względem charakterystyki epidemiologicznej do grupy chorych na SSc. Parametry anatomiczne lewej komory i frakcja wyrzutowa były prawidłowe i porównywalne w obu grupach, natomiast wskaźnik Tei był istotnie wyższy w grupie A ( $0,8 \pm 0,04$  vs.  $0,28 \pm 0,07$ ;  $p < 0,01$ ). Maksymalna prędkość ruchu miokardium S w tkankowej echokardiografii dopplerowskiej była zmniejszona w grupie A w porównaniu z grupą B ( $5,6 \pm 0,5$  vs.  $9,30 \pm 0,5$ ;  $p < 0,01$ ). Również globalne odkształcenie podłużne było mniejsze u chorych na SSc ( $-11 \pm 0,4$  vs.  $-18 \pm 0,3$ ;  $p < 0,01$ ). Nie stwierdzono istotnej różnicy w wartości współczynnika E/A, jednak w grupie A wykryto dysfunkcję rozkurczową lewej komory na podstawie wyższych współczynników E/Ea i E/Vp niż w grupie B (odpowiednio  $13 \pm 1,8$  vs.  $6 \pm 1,6$ ;  $p < 0,01$  i  $2,2 \pm 0,6$  vs.  $1,5 \pm 0,6$ ;  $p < 0,01$ ). Ponadto w grupie A zaobserwowano dłuższy czas trwania Ap–Am ( $\geq 20$  ms) oraz większą objętość lewego przedsionka. Średnia wartość ciśnienia w tętnicy płucnej wynosiła  $37,9 \pm 9$  mm Hg u pacjentów z SSc i  $25 \pm 3$  mm Hg w grupie kontrolnej ( $p < 0,01$ ). Nie stwierdzono dysfunkcji prawej komory.

**Wnioski.** Zajęcie serca w przebiegu SSc poprzedza pojawienie się objawów. Badanie echokardiograficzne z doplerem tkankowym i ocena odkształcenia miokardium w obrazowaniu 2D są pomocne w wykrywaniu zmian w subklinicznym stadium choroby.

Słowa kluczowe: twardzina układowa, zajęcie serca, echokardiografia, porównanie

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### References

1. Ferri C, Valentini G, Cozzi F, et al. Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)*. 2002; 81(2): 139–153, indexed in Pubmed: [11889413](https://pubmed.ncbi.nlm.nih.gov/11889413/).
2. Allanore Y, Kahan A. L'atteinte cardiaque de la sclérodemie systémique. *La Presse Médicale*. 2006; 35(12): 1938–1942, doi: [10.1016/s0755-4982\(06\)74928-4](https://doi.org/10.1016/s0755-4982(06)74928-4).
3. Beranek JT. Pathogenesis of heart fibrosis in systemic sclerosis. *Int J Cardiol*. 2001; 80(2–3): 261–262, doi: [10.1016/s0167-5273\(01\)00490-9](https://doi.org/10.1016/s0167-5273(01)00490-9), indexed in Pubmed: [11676389](https://pubmed.ncbi.nlm.nih.gov/11676389/).

4. André K. L'atteinte myocardique primitive de la sclérodémie systémique. *Bull Acad Méd.* 2011; 195(1): 69–77.
5. D'Angelo WA, Fries JF, Masi AT, et al. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med.* 1969; 46(3): 428–440, indexed in Pubmed: [5780367](#).
6. Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: a controlled study of 100 consecutive patients. *Arthritis Rheum.* 2008; 58(6): 1803–1809, doi: [10.1002/art.23463](#), indexed in Pubmed: [18512815](#).
7. Maione S, Valentini G, Giunta A, et al. Evaluation of cardiac structures and function in systemic sclerosis by Doppler echocardiography. *Cardiology.* 1991; 79(3): 165–171, doi: [10.1159/000174876](#), indexed in Pubmed: [1769033](#).
8. Valentini G, Vitale DF, Giunta A, et al. Diastolic abnormalities in systemic sclerosis: evidence for associated defective cardiac functional reserve. *Ann Rheum Dis.* 1996; 55(7): 455–460, indexed in Pubmed: [8774164](#).
9. Candell-Riera J, Armadans-Gil L, Simeón CP, et al. Comprehensive noninvasive assessment of cardiac involvement in limited systemic sclerosis. *Arthritis Rheum.* 1996; 39(7): 1138–1145, doi: [10.1002/art.1780390710](#), indexed in Pubmed: [8670322](#).
10. Plazak W, Zabinska-Plazak E, Wojas-Pelc A, et al. Heart structure and function in systemic sclerosis. *Eur J Dermatol.* 2002; 12(3): 257–262, indexed in Pubmed: [11978567](#).
11. Allanore Y, Meune C, Vignaux O, et al. Bosentan increases myocardial perfusion and function in systemic sclerosis: a magnetic resonance imaging and tissue-Doppler echography study. *J Rheumatol.* 2006; 33(12): 2464–2469, indexed in Pubmed: [17080515](#).
12. Uematsu M, Nakatani S, Yamagishi M, et al. Usefulness of myocardial velocity gradient derived from two-dimensional tissue Doppler imaging as an indicator of regional myocardial contraction independent of translational motion assessed in atrial septal defect. *Am J Cardiol.* 1997; 79(2): 237–241, doi: [10.1016/s0002-9149\(97\)89292-2](#), indexed in Pubmed: [9193038](#).
13. Coucelo J, Azevedo J, Felizardo A, et al. Myocardial architecture, texture and left ventricular heterogeneity in the pulsed Doppler tissue imaging pattern. *Rev Port Cardiol.* 2000; 19(2): 217–224, indexed in Pubmed: [10763351](#).
14. Rosato E, Maione S, Vitarelli A, et al. Regional diastolic function by tissue Doppler echocardiography in systemic sclerosis: correlation with clinical variables. *Rheumatol Int.* 2008; 29(8): 913–919, doi: [10.1007/s00296-008-0827-x](#).
15. Fernandes F, Ramires FJ, Arteaga E, et al. Cardiac remodeling in patients with systemic sclerosis with no signs or symptoms of heart failure: an endomyocardial biopsy study. *J Card Fail.* 2003; 9(4): 311–317, doi: [10.1054/jcaf.2003.51](#), indexed in Pubmed: [13680552](#).
16. Ferri C, Bello VDi, Martini A, et al. Heart involvement in systemic sclerosis: an ultrasonic tissue characterisation study. *Ann Rheum Dis.* 1998; 57(5): 296–302, doi: [10.1136/ard.57.5.296](#).
17. Can I, Onat AM, Aytemir K, et al. Detecting subclinical biventricular impairment in scleroderma patients by use of pulsed-wave tissue Doppler imaging. *Tex Heart Inst J.* 2009; 36(1): 31–37, indexed in Pubmed: [19436783](#).
18. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med.* 2006; 173(9): 1023–1030, doi: [10.1164/rccm.200510-16680C](#), indexed in Pubmed: [16456139](#).
19. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis.* 2003; 62(11): 1088–1093, indexed in Pubmed: [14583573](#).
20. de Groote P, Millaire A, Foucher-Hossein C, et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol.* 1998; 32(4): 948–954, doi: [10.1016/s0735-1097\(98\)00337-4](#), indexed in Pubmed: [9768716](#).