Assessment of left and right ventricular diastolic function in patients with systemic sclerosis

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Abstract

Background: Systemic sclerosis (SSc) is a connective tissue disease characterised by vascular changes and immunologically induced fibrosis of the skin and internal organs. Systemic sclerosis may be associated with both right (RV) and left ventricular (LV) diastolic dysfunction.

Aim: To analyse RV and LV myocardial diastolic function in patients with SSc and its relation to exercise capacity.

Methods: We prospectively studied 51 consecutive patients (47 females, 4 males, age 53.3±15.2 years) with SSc (mean disease duration 9±12.4 years) and a group of 31 age-matched healthy subjects (28 females, 3 males, age 52.8±12.1 years). In addition to conventional investigation, transthoracic echocardiography (TTE) for assessment of RV and LV myocardial diastolic function and 6-minute walking test (6MWT) were performed.

Results: Abnormal LV filling, as expressed by an inverted mitral E/A ratio (Mit E/A <1), was detected in 28 (55%) SSc patients and in 8 (25%) controls (p <0.001). The mean value of Mit E/A in the SSc group was lower than in controls (1.0±0.3 vs. 1.2±0.3, p=0.04). There were no differences in pulmonary venous flow between SSc patients and controls. The mean value of Tei index for the LV was higher in SSc than in controls (0.35±0.07 vs. 0.29±0.03, p <0.001). Patients with SSc were found to have an inverted Tr E/A ratio (Tr E/A <1), indicating abnormal RV filling. The mean value of Tr E/A in SSc was lower than in controls (0.44±0.08 vs. 0.38±0.05, p <0.001). Abnormal RV filling, as expressed by an inverted tricuspid E/A ratio (TR E/A <1), was detected in 16 (31%) SSc patients and in 5 (16%) controls (p <0.001). The mean value of Tei index for the RV was higher in SSc patients than in controls (0.35±0.07 vs. 0.29±0.03, p <0.001). In multiple regression analysis Tr E/A ratio was independently correlated with Mit E/A ratio (r=0.65, p=0.01).

Conclusions: Impaired RV and LV relaxation is observed in a significant percentage of SSc patients and is associated with decreased exercise capacity.

Key words: systemic sclerosis, diastolic function, echocardiography, 6 minutes walking test

Introduction

Systemic sclerosis (SSc) is a connective tissue disease with typical changes in microcirculation, massive collagen deposition and presence of circulating specific antibodies [1]. During its course, extensive fibrous degeneration develops in many internal organs, including the heart. Severity of cardiac and pulmonary involvement is one of the major factors having an adverse impact on clinical course and prognosis in patients with SSc [2]. The most fatal cardiovascular complications during SSc course include pulmonary hypertension and arrhythmias or conduction disturbances [3]. Pathogenesis of organ complications in patients with SSc suggests the possibility of diastolic performance...
impairment of both ventricles. However, there have been no studies published so far regarding the relation between exercise capacity and diastolic function of both ventricles.

The purpose of this study was to analyse diastolic performance of both ventricles using echocardiography in patients with SSc and to correlate the echocardiographic parameters with evaluated functional indices.

Methods

This prospective study involved 51 consecutive patients (47 females and 4 males; mean age of 53.3±15.2 years) with detected SSc (mean disease duration of 9±12.4 years, range 1 to 45 years, median 6 years). A diagnosis of SSc was established according to the criteria of the American Rheumatism Association [4]. In 29 (57%) patients diffuse form of systemic sclerosis (dSSc) was diagnosed whereas the limited form of the disease (lSSc) was detected in the remaining subjects.

Patients presenting with symptoms and signs of coronary artery disease, arterial hypertension, left ventricular (LV) hypertrophy assessed by echocardiography, or valvular heart disease were excluded from the study. Moreover, patients with significant respiratory function impairment defined as forced vital capacity (FVC), total lung capacity (TLC) and/or first-second forced expiratory volume (FEV₁) <60% of normal predicted value were also excluded from further clinical analysis. Impaired renal function with creatinine concentration >1.2 mg/dl was an additional excluding criterion.

Patients did not receive beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II (AT II) receptor blockers, diuretics, calcium channel blockers or aldosterone antagonists at the time of examination.

During the study, 3 patients were treated with glucocorticosteroids, and immunosuppressive drugs were necessary in 1 case due to SSc progression. The majority of patients with SSc received additionally, as recommended by dermatologists, vitamin A and/or E and agents with a potentially beneficial impact on microcirculation such as pentoxifylline or bencyclane/buflomedil (20 and 31 patients, respectively).

A control group involved 31 healthy individuals (28 women, 3 men; mean age of 52.6±12.1 years). All patients with SSc and control subjects expressed informed consent to participate in the study and the study protocol was approved by the Bioethical Committee of the Medical University of Warsaw.

Assessment of systolic function

Left ventricular ejection fraction (LVEF) was calculated according to Simpson’s formula employing a two-dimensional image of the LV chamber during systole and diastole in the four- and two-chamber apical views [6].

Assessment of left and right atrial dimensions

Both upper to lower and medial to lateral dimensions of the left and right atrium were measured on two-dimensional images from apical four-chamber view at the end of systole.

Analysis of LV diastolic performance

Mitrval valve inflow (MVF) was recorded in the apical four-chamber view with Doppler gate positioned in the LV on the level of the mitral valve edges. The following parameters were evaluated: peak velocity of the early inflow phase (E), peak velocity of the atrial inflow phase (A), E/A ratio and phase E deceleration time (DT). The apical five-chamber view enabled simultaneous registration of the flow pattern through aortic and mitral valves and then isovolumetric diastolic time (IVRT) was calculated. The pattern of the right upper pulmonary vein inflow (PVF) was recorded from the apical four-chamber view after the Doppler gate was positioned approximately 1 cm inside the vein. The following parameters were evaluated: peak systolic inflow velocity (S), peak diastolic inflow velocity (D), S/D ratio and peak velocity of regurgitated atrial flow (Ar) (Figure 1). To confirm physiological left atrial (LA) pressure the following values were considered normal: E/A 1-2, DT 160-240 ms, IVRT 70-90 ms, S>D and Ar <0.35 cm/s [7, 8].

Echocardiography

Echocardiography was performed using a Hewlett-Packard SONOS 2000 device (Andover, Massachusetts) equipped with a 2 MHz probe. The study protocol (views and measurements) complied with the Guidelines of the Echocardiographic Section of the Polish Cardiac Society [5]. Examinations were recorded on S-VHS video tapes. Measurements were performed for three consecutive heart cycles in each patient recorded on expiration. Analysis of echocardiographic recordings was carried out by two independent observers.

Evaluation of LV systolic function

Left ventricular ejection fraction (LVEF) was calculated according to Simpson’s formula employing a two-dimensional image of the LV chamber during systole and diastole in the four- and two-chamber apical views [6].
Assessment of left and right ventricular diastolic function in patients with systemic scleroderma

Assessment of global LV function

Index of LV efficiency (Tei index) as a sum of isovolumetric systole and diastole time to LV ejection time ratio was calculated according to the method proposed by Tei et al. Normal value for the LV was assumed to be 0.39±0.05 [9] (Figure 2).

Evaluation of right ventricular diastolic function

Inflow to the right ventricle (RV) through the tricuspid valve was recorded in the apical four-chamber view with Doppler gate positioned in the RV on the level of the tricuspid valve leaflet edges. Peak velocity of the early inflow phase (E), peak velocity of the atrial inflow phase (A) and E/A ratio were evaluated. A value of E/A ratio >1 was considered normal [10].

Assessment of global RV performance

Index of RV efficiency (Tei index) was calculated according to the method proposed by Tei et al. Normal value for the RV was assumed to be 0.28±0.04 [11].

Measurement of RV systolic pressure

Peak velocity of the tricuspid regurgitation flow was recorded in the apical four-chamber view using continuous wave Doppler. Employing simplified Bernoulli equation, tricuspid regurgitation peak gradient (TRPG) was calculated. Pulmonary hypertension was diagnosed if TRPG exceeded 31 mmHg (or peak velocity of tricuspid regurgitation flow >2.8 m/s) [12].

6-minute walking test (6MWT)

Every patient with SSc and of the control group underwent 6MWT. This examination was carried out in the hospital corridor under physician supervision. Before as well as just after the test, heart rate, arterial pressure and capillary blood pressure saturation using a pulse oximetry device were recorded. Also, desaturation of capillary blood: ∆sat (saturation prior to study – saturation after study) was registered. Distance covered during 6MWT was recorded [13].

Statistical analysis

Statistical significance of differences between the two groups regarding variables following a normal distribution was evaluated by means of the unpaired Student’s t test. Mann-Whitney U test was used if the examined variables did not follow a normal distribution. The differences of qualitative variables between the two examined groups were assessed by means of χ² test with Yates’ correction, if necessary. The power of correlation between variables was assessed using Pearson or Spearman analysis of correlation. A p value <0.05 was considered statistically significant for all calculations. The results are expressed as the mean and standard deviation.

Results

General characteristics of 51 patients with SSc and 31 individuals in the control group are outlined in Table I. Patients in the examined group did not differ from healthy subjects regarding demographic parameters, although they had slightly lower body mass index. Moreover, no significant differences with respect to hypertension were noted. In patients with SSc, higher resting heart rate was found compared with subjects of the control group.

The parameters of respiratory system function are summarised in Table II.

Echocardiographic assessment

In all patients with SSc and in the control group, normal LV performance was observed. Mean LVEF did not differ significantly between the examined groups of patients (65±5.1 vs. 65.1±3.2%, NS).

In patients with SSc and in the control group, no significant differences in LA either upper to lower or medial to lateral dimension (43.6±6.1 vs. 42.3±5.1 mm;
p=0.3 and 36.5±3.8 vs. 36±4.1 mm; p=0.56, respectively) were noted. Also, no differences between corresponding right atrial dimensions were found (42.8±5.2 vs. 40.1±4.8 mm; p=0.1 and 35.4±4.6 vs. 3.2±3.7; p=0.2, respectively).

The echocardiographic parameters of LV diastolic function are presented in Table III. Impaired LV relaxation defined as E/A ratio of the mitral inflow <1 was observed in 28 (55%) patients with SSc and in 8 (26%) of the control group (p <0.001). The E/A ratio was significantly lower in patients with SSc than in subjects in the control group. No marked differences between the two groups with respect to the parameters of pulmonary vein inflow were observed. However, significantly higher mean values of Tei index were seen in SSc patients compared to controls. The echocardiographic parameters of RV diastolic performance are presented in Table IV. Patients had significantly higher mean values of Tei ratio and lower E/A ratio values than healthy individuals. Additionally, a significant strong positive correlation between Tr E/A and Mit E/A (r=0.65, p=0.01) was found. Regarding Tei index for the LV and RV no such correlation was documented. No correlations of parameters of ventricular diastolic function and other echocardiographic variables such as TRPG or LVEF were observed.

Tricuspid regurgitation was found in 41 (80.4%) patients with SSc and in 9 (29%) healthy individuals of the control group (p <0.001). Peak systolic tricuspid pressure gradient exceeded 31 mmHg in 13 (25%) patients with SSc, while in all subjects in the control group TRPG was below this threshold. Thus, mean TRPG was significantly higher in patients with SSc than in the control group (26.7±7.3 vs. 19.3±4.1 mmHg; p=0.005).

6-minute walking test

The findings of 6MWT are outlined in Table V. Mean distance covered during 6MWT was significantly lower in patients with SSc than in the control group. Markedly lower capillary blood saturation was noted in the SSc group than in the control one either before examination or immediately after 6MWT completion. Moreover,
Discussion

Cardiovascular complications in patients with SSc are among the major factors determining clinical outcome. Recently, many reports evaluating prevalence of pulmonary hypertension and clinical relevance of RV pressure overload in this group of patients have been published [14-17]. However, so far only a few studies assessing diastolic performance of both ventricles in patients with SSc have been reported [18-21]. The available literature lacks studies assessing correlations between diastolic ventricular function and parameters of exercise capacity in this group of patients. In our study, significant disturbances of diastolic function and impaired relaxation of the type involving both LV and RV were noted in patients with SSc. Moreover, patients with SSc had significantly lower E/A ratio of mitral and tricuspid inflow compared with enrolled control group subjects. The decrease in this ratio resulted from significantly increased velocities of end-diastolic inflow waves for both ventricles.

Due to a higher incidence of increased TRPG and the possibility of silent changes within the pulmonary circulation, isolated impairment in RV diastolic function could be expected [19, 21]. In our study however, coexistence of similar abnormalities in the LV was noted. This finding may indicate a process involving the myocardium of both ventricles. Diastolic performance abnormalities of LV impaired relaxation type with E/A index <1 were noted in 55% of examined patients with SSc. Our results are consistent with the findings reported by other authors [22]. Gülülü et al. and D’Andrea et al., employing evaluation of both Doppler inflow and tissue Doppler echocardiography, showed impairment of LV and RV diastolic function in patients with SSc [23, 24]. Similarly, Lindqvist et al. found impairment of RV performance in patients with SSc [21].

Pathogenesis of cardiac changes in patients with SSc is not clearly understood. Myocardial fibrosis is thought to be one of the most important pathological changes during SSc course. It is caused by increased activity of fibroblasts, deposition of excess extracellular fibrous tissue matrix containing a large number of collagen fibres, and lesions in the small blood vessels [25]. Bulkeley et al. revealed myocardial fibrosis in 23 (44%) out of 52 patients with SSc who underwent autopsy [26]. Myocardial fibrosis in SSc was also found by other authors [27, 28]. However, myocardial fibrosis would be expected to cause impaired compliance expressed as pathological increase in E/A or shortening of E wave deceleration time [7, 29]. In our study we observed opposite changes of E/A, and deceleration duration did not differ significantly between the examined groups. Of note, patients with pulmonary fibrosis were not enrolled in our study, and including them would increase indices of RV afterload and impaired performance. It is well known that diastolic function disturbances of LV impaired relaxation type are noted also in patients with coronary artery disease as a result of myocardial ischaemia [29]. In our opinion, abnormalities of myocardial perfusion may represent a potential mechanism responsible for changes typical for the impairment of ventricular relaxation in our examined patients. It is known that during SSc course, myocardial ischaemia may cause a spasm of the small coronary vessels that resembles Raynaud syndrome. Additionally, inflammatory changes and fibrosis within the coronary artery wall may also limit cardiac perfusion [25].

Assessing LV diastolic function we also employed an analysis of pulmonary vein inflow, which did not differ significantly between patients with SSc and healthy individuals. Similar results were published by Gülülü et al., who did not observe any significant differences in the parameters of pulmonary vein inflow in patients with SSc and in healthy subjects [23].

In our study, RV and LV global function by means of Tei index analysis was also assessed. Up to now, it has been reported that heart rate, RV pressure and dimension as well as presence of tricuspid regurgitation did not impact on this index value [11]. We revealed statistically significant worse RV as well as LV global function in patients with SSc compared with the control group. Gülülü et al. noted significantly higher Tei index values for LV in patients with SSc than in control individuals (0.49±0.19 vs. 0.42±0.007; p=0.024). This was in contrast to the difference of Tei index value for RV, which did not reach statistical significance (0.34±0.18 vs. 0.26±0.06; NS) [23]. Hsiao et al. calculated the value of this index using Doppler echocardiography in 40 patients with SSc and 45 healthy volunteers. They found a significant increase of Tei index for the RV (0.41±0.06 vs. 0.51±0.06;
Patients with SSc enrolled in our study had worse exercise capacity than control group subjects. During 6MWT they covered a significantly shorter distance and capillary blood desaturation was more pronounced than in healthy control individuals. We also noted a significant positive correlation between Tr E/A or Mit E/A and distance walked during 6MWT. Impaired diastolic performance may limit the exercise capacity of patients with SSc and the correlation found in our study may represent proof of such a thesis. Pulmonary hypertension observed in 13 (25%) patients and even subclinical pulmonary fibrosis in patients with SSc may however limit exercise capacity as well.

**Study limitations**

Tissue Doppler echocardiography, currently accepted as a modern diagnostic approach in diastolic function assessment, was not carried out in our group of patients with SSc. This was caused by our initial technical limitations. Nowadays, every patient undergoes tissue Doppler echocardiography, which in future will enable more detailed assessment of diastolic function in patients with systemic scleroderma. In patients with pulmonary hypertension detected by echocardiography, no cardiac catheterisation was carried out to confirm diagnosis of pulmonary hypertension and haemodynamic changes because only mild pulmonary hypertension cases were observed.

**Conclusions**

Patients with systemic sclerosis manifest impaired diastolic function (of relaxation impairment type) of both ventricles. Depressed diastolic function may contribute to the limitation of exercise capacity in this group of patients.

**References**

Assessment of left and right ventricular diastolic function in patients with systemic scleroderma

Ocena funkcji rozkurczowej lewej i prawej komory serca u pacjentów z twardziną układową

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Streszczenie

Wstęp: Twardzina układowa (ang. systemic sclerosis, SSc) jest chorobą tkanki łącznej, charakteryzującą się zmianami w mikrokrążeniu, masowym odkładaniu się kolagenu oraz obecnością swoistych przeciwciał. Równocześnie z zajęciem skóry rozwijają się rozległe zmiany włókniste w narządach wewnętrznych, w tym również w sercu. Patogeneza powikłań narządowych u chorych z SSc sugeruje możliwość upośledzenia funkcji rozkurczowej obu komór serca.

Cel: Analiza echokardiograficzna funkcji rozkurczowej komór serca u chorych z SSc oraz próba powiązania parametrów echokardiograficznych ze wskaźnikami oceniającymi wydolność fizyczną.

Metodyka: Prospektowymi badaniami objęto 51 kolejnych chorych (47 kobiet, 4 mężczyzn, średni wiek 53,3±15,2 roku) z rozpozaną SSc (średni czas trwania choroby 9±12,4 roku). Grupę kontrolną stanowiło 31 zdrowych osób (28 kobiet, 3 mężczyzn, średni wiek 52,6±12,1 roku). W obu grupach przeprowadzono badanie echokardiograficzne przez ścianę klatki piersiowej (TTE) ze szczególną oceną funkcji rozkurczowej lewej (LV) i prawej komory serca (RV) oraz test 6-minutowego marszu (6MWT).

 Wyniki: Chorzy z grupy badanej oraz kontrolnej nie różnili się pod względem parametrów demograficznych. Upośledzoną relaksację LV, wyrażoną jako E/A napływu mitralnego <1 (Mit E/A), obserwowano u 28 (55%) chorych z SSc i u 8 (26%) z grupy kontrolnej (p <0,001). U chorych z SSc stwierdzono istotnie statystycznie niższy stosunek Mit E/A niż u badanych z grupy kontrolnej (1,0±0,3 vs 1,2±0,3, p=0,04). Nie stwierdzono znamiennych różnic pomiędzy grupami w parametrach napływu z żył płucnych. Wykazano istotnie statystycznie większe średnie wartości indeksu Tei dla LV u chorych z SSc niż u badanych z grupy kontrolnej, które wynosiły odpowiednio 0,44±0,08 vs 0,38±0,05, p <0,001. Upośledzoną relaksację RV odzwierciedloną jako E/A napływu trójdzielnego <1 (Tr E/A) wykazano u 16 (31%) chorych z SSc i 5 (16%) z grupy kontrolnej (p <0,001). U chorych z SSc stwierdzono istotnie niższy stosunek Tr E/A niż u badanych z grupy kontrolnej (1,0±0,2 vs 1,2±0,3, p=0,04). U chorych z grupy badanej wykazano ponadto znamienne większe średnie wartości indeksu Tei dla RV niż u badanych z grupy kontrolnej (0,35±0,07 vs 0,29±0,03, p <0,001). Stwierdzono istotną dodatnią korelację pomiędzy Tr E/A i Mit E/A (r=0,65, p=0,01). Średni dystans przebyty podczas 6MWT był istotnie krótszy u chorych z SSc niż u badanych z grupy kontrolnej (528±100,6 vs 617±80 m, p <0,001). Upośledzone wydolność fizyczną cechuje upośledzenie wydolności serca. Wśród chorych z SSc stwierdzono istotnie niższe wartości saturacji kapilarnej niż u osób zdrowych, które wynosiły odpowiednio 95,9±4,24 vs 98±1%, p<0,01 oraz 92,7±4,9 vs 97,2±1,2%, p<0,001. Ponadto wykazano istotnie większe desaturację kapilarną (∆sat %) po 6MWT u chorych z SSc (3,4±3,1 vs 0,7±0,9, p <0,001). Warto podkreślić, że stwierdzono istotnie statystycznie większe wskaźniki E/A dla LV u chorych z SSc niż u osób zdrowych, które wykazują istotną dodatnią korelację pomiędzy Mit E/A a Mit E/A (r=0,73, p=0,01). Średni dystans przebyty podczas 6MWT był istotnie krótszy u chorych z SSc niż u osób zdrowych, które wykazują istotną dodatnią korelację pomiędzy Mit E/A a Mit E/A (r=0,73, p=0,01). Warto podkreślić, że stwierdzono istotnie statystycznie większe wskaźniki E/A dla LV u chorych z SSc niż u osób zdrowych, które wykazują istotną dodatnią korelację pomiędzy Mit E/A a Mit E/A (r=0,73, p=0,01).

Wnioski: Chorych z SSc cechuje upośledzenie wydolności rozkurczowej obu komór serca o typie zaburzeń relaksacji. Upośledzenie funkcji rozkurczowej może mieć wpływ na ograniczenie wydolności wysiłkowej w tej grupie chorych.

Słowa kluczowe: twardzina układowa, funkcja rozkurczowa, echokardiografia, test 6-minutowego marszu

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