Original article

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Diastolic heart dysfunction, increased pulmonary capillary wedge pressure and impaired exercise tolerance in patients with systemic sclerosis

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Abstract

Background: Diastolic heart dysfunction, responsible for dyspnoea in heart failure patients, is an important prognostic factor. Patients with systemic sclerosis (SSc) serve as a model of diastolic heart failure with preserved ejection fraction.

Aim: To quantify diastolic left ventricular (LV) dysfunction and elevation of pulmonary capillary wedge pressures (PCWP) in SSc patients and to assess the effects of these parameters on exercise tolerance.

Methods: In 46 SSc patients (43 females, three males, aged 24–73 years) and 30 healthy females, echocardiography with tissue Doppler (TDE) and cardiopulmonary exercise tests (CPX) were performed. During TDE, the systolic (S) and early diastolic (E) velocities of mitral annulus were recorded. The PCWP was calculated on the basis of mitral inflow E velocity and E velocity of mitral annulus. The CPX was performed using a modified Bruce protocol.

Results: Left ventricular ejection fraction was normal in the SSc group. Mitral inflow E/A ratio was pseudonormal in five SSc patients, and significantly decreased in the remainder as compared to controls (0.87 ± 0.2 *vs* 1.38 ± 0.5, $p < 0.0002$). The TDE examination confirmed normal systolic LV function, but severe LV diastolic dysfunction (E 8.66 ± 2.5 cm/s *vs* 12.39 ± ± 3.5 cm/s in controls, $p < 0.000002$). The PCWP was higher in the SSc group (11.8 ± 3.3 mm Hg *vs* 7.7 ± 1.7 mm Hg in controls, $p < 0.0001$). The PCWP > 10 mm Hg significantly decreased exercise duration, maximal oxygen uptake and carbon dioxide output and identified patients with oxygen uptake < 20 mL/kg/min with 100% sensitivity and 78% specificity. The ventilatory equivalent of carbon dioxide was increased in the SSc group (VE/VCO_2 38.7 ± 7.5 *vs* 30.55 ± 4.2 in controls, $p < 0.002$).

Conclusions: Pure LV diastolic dysfunction, typical of SSc, leads to the elevation of PCWP. Values of PCWP > 10 mm Hg are associated with severe exercise intolerance demonstrated by shorter duration of exercise with decreased oxygen uptake and carbon dioxide output during exercise.

Key words: cardiopulmonary exercise test, diastolic dysfunction, pulmonary capillary wedge pressure, systemic sclerosis

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INTRODUCTION

Diastolic heart dysfunction is the primary mechanism responsible for dyspnoea in heart failure (HF) patients and an important prognostic factor irrespective of the presence of systolic dysfunction [1]. The crucial role is played by two factors: the severity of diastolic left ventricular (LV) disturbances, and the (objectively measured) degree of exercise intolerance.

An echocardiographic assessment of LV diastolic function based on mitral inflow has several limitations, the most important being the dependence of mitral inflow on left atrial

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pressure. An increase in the left atrial pressure overrides the effects of impaired relaxation, often resulting in a pseudonormalisation of the transmitral velocity [2]. Tissue Doppler echocardiography (TDE) enables an accurate diagnosis of systolic and diastolic LV disturbances [3]. The velocity of mitral annulus during early diastole is less dependent on left atrial pressure and does not show the pseudonormalisation effect. Based on an examination of early mitral inflow (standard Doppler method) and early mitral annulus velocity (TDE), the pulmonary capillary wedge pressure (PCWP) may be measurred [2], which reflects the influence of diastolic LV disturbances on pulmonary circulation and, in effect, dyspnoea. The objective method of exercise intolerance quantification is a cardiopulmonary exercise test (CPX) [4].

Systemic sclerosis (SSc) is a multisystem disorder characterised by excessive accumulation of collagen and fibrotic changes in many organs, including the heart [5]. Systemic sclerosis could serve as a model of diastolic LV dysfunction with preserved systolic function [6]. Heart involvement strongly influences prognosis by shortening the survival of SSc patients [7–9]. For this reason, an accurate assessment of cardiac abnormalities in SSc plays an important role in patient evaluation.

The aim of this study was to non-invasively quantify the diastolic LV dysfunction and elevation of PCWP in SSc patients, and to assess their effect on exercise tolerance.

METHODS

Study group

Two groups of individuals were examined: 46 consecutive SSc patients and 30 healthy controls. The patients group consisted of 43 females and three males aged 24–73 (mean age 55.4 years). In 25 (54.3%) of them, limited SSc was diagnosed, and in the other 21 (45.7%) a diffuse SSc was present. The duration of the disease at the time of examination was 2–32 years (mean 15.5 years). The Scl-70 autoantibodies were found in 32 patients, anti-centromere in 12, and other types in ten (anti-fibrillarin, Ku, Ro, antimitochondrial). Physical examination revealed arterial hypertension in three patients. Dyspnoea at rest was not present in any of the patients. The results of peripheral blood count, serum levels of sodium, potassium, glucose, creatinine and urinalysis were within the normal ranges. The patients were treated with (number; %): pentoxyphilline (32; 69.6%), calcium antagonists (14; 30%), cinnarizine (eight; 17.4%), nicergoline (five; 10,9%), sadamine (eight; 17.4%), bencyclane (five; 10.9%), prednisone (six; 13%), angiotensin converting enzyme (ACE) inhibitors (14; 30.4%), diosmine (ten; 21.7%), ranitidine (six; 13%) and hydroxizine (ten; 21.7%).

The control group consisted of 30 healthy females aged 38–57 (mean age 51.6 years) with normal blood pressure and ECG, and without any pathologies in physical examination. The age of control subjects and SSc patients was similar.

In all the patients, and in the control group, echocardiography with TDE, spirometry and CPX were performed. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the Ethical Committee of the Jagiellonian University in Krakow.

Echocardiography

The data obtained from echocardiographic examination (Toshiba Aplio SSA-770 Ultrasound System, Toshiba, Japan) included: LV diastolic and systolic dimension, LV ejection fraction (Simpson method), the thickness of LV walls in diastole, E and A mitral inflow velocity, valvular pressure gradients, and regurgitation assessment. During TDE examination, the velocities of mitral annulus were recorded from a four-chamber view during systole (S velocity) and early diastole (E velocity).

Right ventricular systolic pressure (RVSP) was calculated from the velocity of tricuspid regurgitant jet (V_{tr}) according to the equation RVSP = 4 V_{tr} + RAP mm Hg, where RAP represents right atrial pressure, estimated as 5 or 10 mm Hg due to inferior vena cava and right atrium diameters. Pulmonary capillary wedge pressure was calculated based on the formula: PCWP = 1.24 E_m/E_{tde} + 2, where E_m represents the velocity of mitral E inflow (measured by classic continuous wave Doppler) and E_{tde} represents the early diastolic velocity of mitral annulus (measured by TDE in four-chamber view) [2].

Cardiopulmonary treadmill exercise tests

The CPX (Marquette Series 2000 Case 16 Treadmill, GE Marquette, USA) was performed using a modified Bruce protocol. Before CPX, spirometric examinations were also performed. During the test, ECG, blood pressure, clinical symptoms and duration of exercise were recorded. The gas parameters monitored included: maximal oxygen uptake (VO_2, mL/kg/min), maximal carbon dioxide output (VCO_2, mL/kg/min), ventilatory equivalent of oxygen (VE/VO_2, the ratio of minute ventilation and VO_2), ventilatory equivalent of carbon dioxide (VE/VCO_2, the ratio of minute ventilation and VCO_2), oxygen partial pressure measured in exhaled air (PET O_2), carbon dioxide partial pressure in exhaled air (PET CO_2) and the time of anaerobic threshold (AT), i.e. the stage of exercise at which anaerobic metabolism starts. Based on VO_2 results, the patients were qualified into four groups of cardiopulmonary failure according to Weber classification [10].

Statistical analysis

Statistical analysis was performed using Statistica Six Sigma software (StatSoft Inc, USA). All numerical data are expressed as mean values ± SD or as proportions. Continuous variables were compared by the use of t-test. The χ^2 test was used to examine differences in proportions. The relationship between PCWP and VO_2 was examined by the use of linear regression with 95% confidence intervals. The level for statistical significance was predetermined at $p < 0.05$.

Table 1. Echocardiographic data of systolic and diastolic left ventricular function in systemic sclerosis (SSc) patients and control subjects

	SSc patients	Control group	P
Left ventricular ejection fraction [%]	67.4 ± 9.4	68.8 ± 6.1	NS
Mitral inflow E/A ratio	0.87 ± 0.2*	1.38 ± 0.5	< 0.0002
TDE S velocity [cm/s]	7.64 ± 1.36	7.95 ± 0.91	NS
TDE E velocity [cm/s]	8.66 ± 2.54	12.39 ± 3.54	< 0.000002

*Data from 41 patients; the data obtained from five patients with pseudonormal mitral inflow was excluded; TDE — tissue Doppler echocardiography; S — systolic velocity of mitral annulus; E — early diastolic velocity of mitral annulus

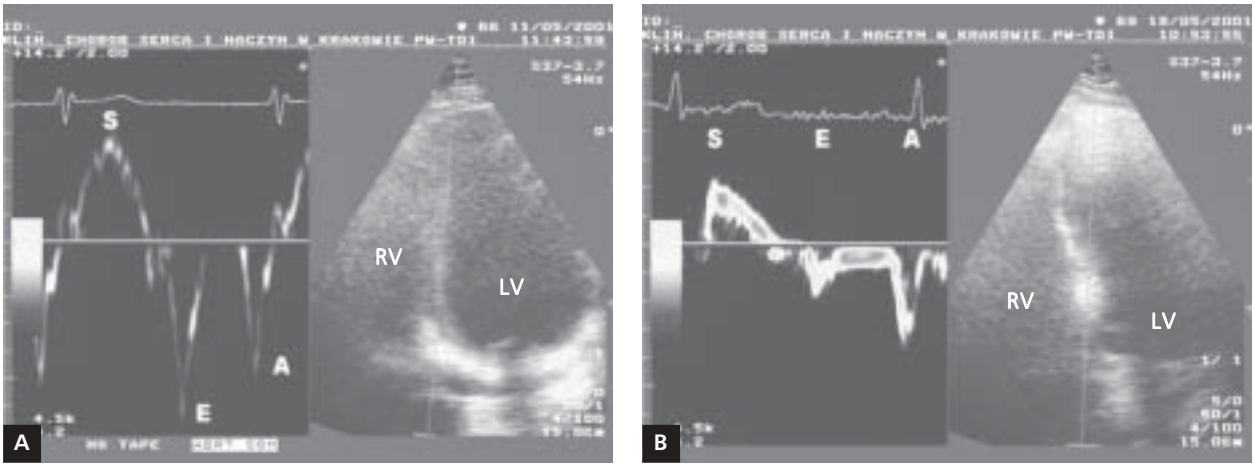

Figure 1. Tissue Doppler echocardiography recording in a healthy person (**A**) and in a systemic sclerosis (SSc) patient (**B**). Note the systolic (S) wave, early diastolic (E) wave and end diastolic (A) wave. In the SSc patient, E velocity is significantly decreased; LV — left ventricle; RV — right ventricle

RESULTS

Echocardiographic examination of SSc patients showed normal systolic LV function. The LV ejection fraction in the SSc group did not differ from that in the control group (Table 1). In contrast, mitral inflow E/A ratio showed significant diastolic LV dysfunction in the whole SSc group; in five patients, pseudonormal inflow pattern was observed, indicating advanced diastolic dysfunction. In the remainder (n = 41), significantly decreased E/A ratio reflected relaxation impairment (Table 1). The TDE examination further confirmed normal systolic LV function with severe LV diastolic dysfunction. The LV diastolic dysfunction was observed in all examined patients during TDE (Table 1, Fig. 1) and was present despite normal LV muscle thickness (intraventricular septum diastolic thickness 9.2 ± 1.9 mm, posterior wall diastolic thickness 9.3 ± 1.4 mm). No signs of significant valvular disturbances were observed, with only mild tricuspid insufficiency in 21 (46%) patients. Tricuspid insufficiency was a result of mild elevation of right ventricular and pulmonary pressures, and not valve disease itself. In 14 (30.4%) patients, mild pulmonary hypertension (pulmonary artery systolic pressure 35–45 mm Hg) was observed; none of the patients showed pulmonary systolic pressure above 45 mm Hg.

Spirometry showed a restrictive ventilatory pattern in the SSc group (Table 2). In cardiopulmonary exercise tests, all the patients showed low exercise tolerance (short duration of exercise) together with decreased time to AT (Fig. 2). The main finding, however, was a severe decrease in maximal oxygen uptake and low carbon dioxide output in the SSc patients (Table 3). Ventilatory equivalent of oxygen and ventilatory equivalent of carbon dioxide were increased in the examined patients, who had to maintain higher ventilation than the control subjects to consume the same amount of oxygen and to exhale the same amount of carbon dioxide (Table 3). This is also the reason for higher oxygen partial pressure measured in exhaled air in the SSc patients (impaired oxygen diffusion to the blood) and lower carbon dioxide partial pressure measured in exhaled air in this group (impaired carbon dioxide diffusion from the blood) (Table 3), severe cardiopulmonary failure (class C and D) was found in 43.5% of patients (Table 4).

The mean PCWP value was significantly higher in the SSc group (11.8 ± 3.3 mm Hg) than in the control group (7.7 ±

Table 2. Spirometry results in systemic sclerosis (SSc) patients and control subjects

	SSc patients	Control group	P
FVC [L]	2.61 ± 0.7	3.55 ± 0.6	< 0.0003
FVC [% of predicted value]	82.1 ± 21.5	106.5 ± 14.8	< 0.0008
FEV_1 [L]	2.17 ± 0.7	2.81 ± 0.4	< 0.003
FEV_1 [% of predicted value]	82.6 ± 21.8	99.2 ± 12.0	< 0.01
FEV_1/FVC [%]	84.2 ± 10.3	78.6 ± 5.2	NS

FVC — forced vital capacity; FEV_1 — forced expiratory volume at one second

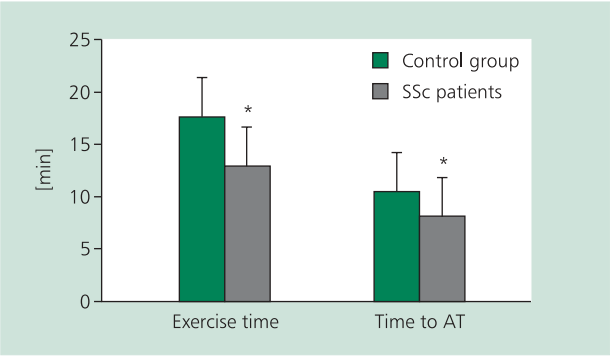

Figure 2. Exercise duration and time to anaerobic threshold (AT) in systemic sclerosis (SSc) patients and control subjects; *p < 0.01 according to the values in control group

± 1.7 mm Hg; p < 0.001). Elevated PCWP strongly influenced exercise capacity in SSc patients. The mean PCWP value of 13.2 ± 3.1 mm Hg distinguished patients with severe exercise intolerance from those with less advanced cardiopulmonary failure, whereas the elevation of PCWP to the mean value of 15.7 ± 0.9 mm Hg identified patients with end-stage cardiopulmonary failure (Weber class D) (Table 4). Negative correlations were found between PCWP and maximal oxygen consumption (Fig. 3, r = –0.61, p < 0.05), amount of carbon dioxide exhaled (r = –0.56, p < 0.05) and duration of exercise (r = –0.76, p < 0.05).

The PCWP > 10 mm Hg significantly decreased exercise duration, maximal oxygen consumption and amount of carbon dioxide production (Fig. 4), and identified patients with oxygen consumption < 20 mL/kg/min with 100% sensitivity and 78% specificity.

The type of disease (limited or diffuse SSc) had no significant effects on the results of echocardiography and CPX.

DISCUSSION

Diastolic HF currently accounts for more than 50% of all HF patients [1]. Moreover, the prognosis in patients suffering from diastolic HF is as poor as in those with systolic HF [11–13].

Table 3. Cardiopulmonary exercise test results in systemic sclerosis (SSc) patients and control subjects

	SSc patients	Control group	P
VO_2max [mL/kg/min]	16.51 ± 6.9	25.66 ± 6.6	< 0.001
VCO_2max [mL/kg/min]	16.59 ± 7.1	27.33 ± 6.7	< 0.0004
VE/VO_2	37.5 ± 8.1	31.36 ± 4.6	< 0.02
VE/VCO_2	38.7 ± 7.5	30.55 ± 4.2	< 0.002
PET O_2	14.22 ± 0.9	13.75 ± 0.5	< 0.05
PET CO_2	4.81 ± 0.9	5.24 ± 0.5	< 0.05

VO_2 — oxygen uptake; VCO_2 — carbon dioxide output; VE/VO_2 — ventilatory equivalent of oxygen: the ratio of minute ventilation and VO_2; VE/VCO_2 — ventilatory equivalent of carbon dioxide: the ratio of minute ventilation and VCO_2; PET O_2 — oxygen partial pressure measured in exhaled air; PET CO_2 — carbon dioxide partial pressure in exhaled air

Table 4. Weber classification of cardiopulmonary failure in systemic sclerosis (SSc) patients

	Weber class A	Weber class B	Weber class C	Weber class D
Number of patients [%]	10 (21.7%)	16 (34.8%)	15 (32.6%)	5 (10.9%)
VO_2 [mL/kg/min]	> 20	16–20	10–15	< 10
PCWP [mm Hg]	8.9 ± 2.4	10.9 ± 2.9*	13.2 ± 3.1**	15.7 ± 0.9**

*p < 0.05; **p < 0.001 according to the values in class A; VO_2 — oxygen uptake; PCWP — pulmonary capillary wedge pressure

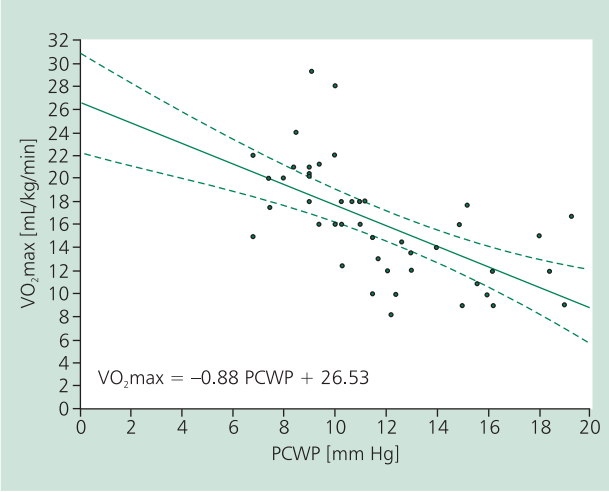

Figure 3. Correlation between pulmonary capillary wedge pressure (PCWP) and maximal oxygen uptake (VO_2max) in systemic sclerosis patients

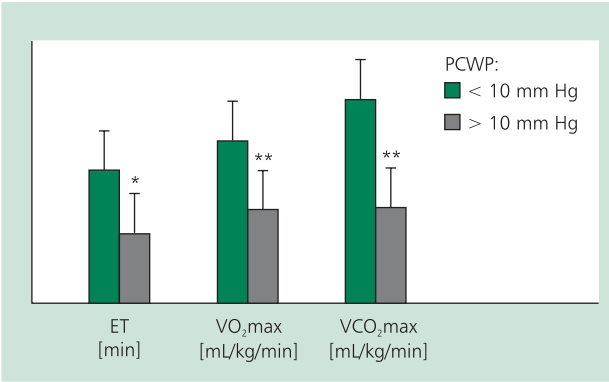

Figure 4. Exercise duration (ET), maximal oxygen uptake (VO_2max) and maximal carbon dioxide output (VCO_2max) in systemic sclerosis patients according to the pulmonary capillary wedge pressure (PCWP); *p < 0.001 and **p < 0.00001

Cardiac involvement in SSc results from fibroblast proliferation and overproduction of collagen [5] and is associated with poor prognosis [8, 9]. Clinically, it is characterised by diastolic LV dysfunction [6, 14, 15], myocardial ischaemia [16, 17] and preserved [6, 14] or only mildly decreased [18] systolic LV function. In our study, systolic LV function was normal in all patients and comparable with healthy controls.

This normal systolic function despite pathological changes in the myocardium may be partially explained by adrenergic overactivity in SSc, manifested by commonly observed sinus tachycardia [19]. In SSc, myocardial ischaemia has often no effect on systolic function, because it results from coronary artery spasm at the level of very small arteries (150 to 500 mm in diameter) and capillary obliteration which leads to the formation of only small regions of ischaemia in an otherwise well-perfused myocardium [17, 20, 21].

Our study showed severe diastolic LV dysfunction confirmed by the TDE technique, which concurs with results published by others [14, 15]. Diastolic dysfunction results mainly from myocardial fibrosis. However, the role of myocardial ischaemia is also important. The diastolic function of the myocardium is very sensitive to ischaemia [22]. Even small regions of low-perfused myocardium may aggravate diastolic dysfunction resulting from fibrosis. An important finding was that diastolic dysfunction was present despite normal LV wall thickness, and was not related to muscle hypertrophy.

After heart involvement, pulmonary pathology is the second significant factor influencing patient prognosis [5]. In this study, mild pulmonary hypertension was present in 30% of the examined group, a figure which is similar to reported in other studies [23, 24]. The extent and severity of pulmonary involvement are not directly correlated with skin changes [24]. The examination of pulmonary involvement in SSc should include: pulmonary systolic pressure estimation (echocardiography) and assessment of interstitial lung fibrosis (high resolution computed tomography). The main functional impairment includes restrictive ventilatory failure, reflected in our study by a significant reduction in forced vital capacity, a finding already shown by Steen et al. [25] and Georgiev et al. [26]. Obstructive ventilatory failure has also been observed, but only in SSc smokers [25].

Objective evidence of reduced exercise performance can be provided by metabolic exercise testing with measurement of peak exercise oxygen consumption and anaerobic threshold. In our study, the duration of CPX in SSc patients was significantly decreased. Diminished exercise capacity was associated with early start of anaerobic metabolism caused by low oxygen supply to the muscles. Such tissue hypoxia in SSc most probably results from pulmonary involvement and circulatory failure. Diminished exercise capacity in SSc has been already shown [23, 27, 28].

Maximal oxygen uptake and carbon dioxide output were decreased in the SSc patients. The importance of pulmonary involvement in SSc is illustrated by a decrease in the ventilatory equivalents of oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) in the study patients as compared to the controls.

Results of CPX are in line with the results of the TDE study. Diastolic HF leads to elevation of PCWP. In our study, PCWP values measured by the TDE technique were significantly increased in SSc patients. Elevation of PCWP > 10 mm Hg identified patients with an abnormal cardiopulmonary test result (Weber class B–D). There is a scarcity of data in literature concerning the effects of PCWP on maximal oxygen consumption. One single study examined this relationship in 51 patients with chronic HF due to dilated cardiomyopathy or ischaemic heart disease [29]. In that study, a reduction in exercise capacity (Weber class B) was observed at higher PCWP values (14.4 ± 8.8 mm Hg) than those measured in our study (10.9 ± 2.9 mm Hg). In the SSc patients with end-stage cardiopulmonary failure (Weber class D), mean PCWP value was

15.7 mm Hg, whereas in dilated cardiomyopathy, or ischaemic heart disease, such patients represented much less advanced HF (Weber class B). Exercise intolerance in SSc may result from both pulmonary gas exchange abnormalities and diastolic heart dysfunction, which may explain why even slight changes in pulmonary circulation lead to a significant decrease in exercise tolerance. In keeping with this, Kovacs et al. [30] showed that even borderline high pulmonary arterial pressure could be associated with decreased exercise capacity in scleroderma.

The results discussed above may have important implications for the treatment of SSc patients. The detection of HF caused by diastolic LV dysfunction should stimulate efforts to limit (if possible) fibrosis progression. Here, the potential role of ACE inhibitors should be emphasised. Recent data showed that angiotensin II influences fibroblasts activity and collagen synthesis [31, 32], i.e. angiotensin II stimulates the expression of transforming growth factor β1 (TGFβ1) gene, and in consequence leads to enhanced collagen synthesis in heart muscle [33]. Sun et al. [34] reported that in the myocardial regions affected by fibrosis, a high level of local angiotensin II production was observed, together with an increase in angiotensin AT1 and TGFβ1 receptors level. In an experimental model of arterial hypertension in rats, chronic treatment with an ACE inhibitor — lisinopril — inhibited fibrosis of interstitial tissue of the heart [35]. The potentially beneficial effect of ACE inhibitors on the diastolic function of the LV, the course of the disease and the prognosis for SSc patients, should all be addressed in future prospective clinical trials.

CONCLUSIONS

Pure diastolic dysfunction of the LV, typical of SSc, leads to elevation of PCWP in some patients. The PCWP values > 10 mm Hg are associated with severe exercise intolerance reflected by shorter duration of exercise with decreased oxygen uptake and diminished carbon dioxide output during exercise.

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Conflict of interest: *none declared*

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Rozkurczowa niewydolność serca, zwiększone ciśnienie zaklinowania w kapilarach płucnych i upośledzona tolerancja wysiłkowa u chorych z twardziną układową

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Streszczenie

Wstęp: Zaburzenia czynności rozkurczowej lewej komory (LV) u chorych z niewydolnością serca, stanowiące istotny niekorzystny czynnik prognostyczny, są przyczyną upośledzenia ich wydolności wysiłkowej. Twardzina układowa (SSc) może służyć jako model niewydolności serca z zachowaną czynnością skurczową LV.

Cel: Celem pracy była ocena stopnia zaawansowania zaburzeń czynności rozkurczowej LV i wzrostu ciśnienia zaklinowania w kapilarach płucnych (PCWP) u chorych z SSc oraz zbadanie wpływu tych zaburzeń na wydolność wysiłkową chorych.

Metody: W grupie 46 osób z SSc (43 kobiety, 3 mężczyzn, w wieku 24–73 lat) oraz 30 zdrowych kobiet dobranych pod względem wieku wykonano badania echokardiograficzne z tkankową echokardiografią dopplerowską (TDE) oraz testy spiroergometryczne (CPX). Podczas TDE wyznaczano prędkość skurczową (S) oraz wczesnorozkurczową (E) pierścienia mitralnego. Wartość PCWP oceniano na podstawie porównania szybkości napływu mitralnego we wczesnym okresie rozkurczu i prędkości pierścienia mitralnego w badaniu TDE w tym okresie; CPX wykonywano w zmodyfikowanym protokole Bruce'a.

Wyniki: Wartość frakcji wyrzutowej LV w grupie SSc była prawidłowa. Badanie napływu mitralnego wykazało jego pseudonormalizację u 5 (10,9%) chorych oraz istotne obniżenie stosunku E/A u pozostałych 41 (89,1%) osób w porównaniu z grupą kontrolną (odpowiednio 0,87 ± 0,2 *v.* 1,38 ± 0,5; $p < 0,0002$). Badanie TDE potwierdziło prawidłową czynność skurczową LV oraz istotne zaburzenia jej czynności rozkurczowej (E 8,66 ± 2,5 cm/s *v.* 12,39 ± 3,5 cm/s w grupie kontrolnej; $p < 0,000002$). Wartość PCWP była podwyższona u chorych z SSc (11,8 ± 3,3 mm Hg *v.* 7,7 ± 1,7 mm Hg w grupie kontrolnej; $p < 0,0001$). Podwyższenie PCWP > 10 mm Hg wpływało istotnie na ograniczenie czasu wysiłku, maksymalnego zużycia tlenu (VO_2max) oraz wydalania dwutlenku węgla, wskazując na VO_2max < 20 ml/kg/min z czułością wynoszącą 100% i swoistością równą 78%. Wartość wentylacyjnego równoważnika dwutlenku węgla w badanej grupie chorych była istotnie podwyższona (VE/VCO_2 38,7 ± 7,5 *v.* 30,55 ± 4,2 w grupie kontrolnej; $p < 0,002$).

Wnioski: Zaburzenia czynności rozkurczowej LV przy zachowanej jej czynności skurczowej, typowe dla SSc, prowadzą do podwyższenia PCWP. Wartość PCWP > 10 mm Hg w tej grupie chorych wiąże się ze znacznym ograniczeniem tolerancji wysiłku przejawiającym się skróceniem czasu wysiłku, obniżeniem maksymalnego zużycia tlenu oraz ilości wydalanego dwutlenku węgla.

Słowa kluczowe: testy spiroergometryczne, zaburzenia czynności rozkurczowej, ciśnienie zaklinowania w kapilarach płucnych, twardzina układowa

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