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*Rare diseases of the heart*

# Influence of disease-related heart pathology on peak oxygen uptake and ventilation/carbon dioxide output ratio in systemic sclerosis and systemic lupus erythematosus patients (RCD code: I-3C)

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## Abstract

**Background:** Exercise capacity is an independent predictor of mortality in the general population. However, available literature has been focused mainly on exercise testing in patients with ischaemic heart failure. Little is known about such testing in generalized autoimmune diseases with their different pathogenesis and sex prevalence. The aim of the study was to assess the influence of disease-related heart pathology on exercise capacity evaluated by cardiopulmonary exercise (CPX) test in systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) patients.

**Methods:** Echocardiography and CPX test were performed in 46 SSc patients, 60 SLE patients and 30 healthy controls.

**Results:** Echocardiography showed normal left ventricle systolic function in all subjects except for 2 (3,3%) SLE patients with enlarged left ventricle. In contrast, diastolic left ventricular dysfunction was found in all SSc patients and in 13 (21,7%) SLE patients. Right ventricle systolic pressures were elevated (>30 mmHg) in 14 (30,4%) SSc and 10 (16,7%) SLE patients. Valvular leaflet or pericardium thickening was observed in 17 (37,0%) SSc and in 38 (63,3%) SLE patients. CPX test showed low exercise capacity in 36 (78,3%) SSc patients, while mean values of gas exchange parameters remained normal in SLE and control groups. In SSc time of exercise was significantly shorter and peak oxygen uptake decreased as compared to healthy subjects (13,1 ±4,8 min vs. 17,8 ±2,6 min, p = 0,01 and 16,51 ±6,86 ml/kg/min vs. 25,66 ±6,62 ml/kg/min, p = 0,001, respectively). Ventilation/carbon dioxide output ratio (VE/VCO2) was increased (>34) in 32 (69,6%) SSc and 4 (6,7%) SLE patients. Weber C or D class of cardiopulmonary failure (severe or end-stage, VO2peak < 15 ml/kg/min) was observed in 20 (43,5%) SSc and only in 2 (3,4%) SLE patients.

**Conclusions:** Exercise intolerance expressed by VO2peak < 15 ml/kg/min and VE/VCO2 > 34 was present in almost half of SSc patients, while severely impaired gas exchange parameters were very rare in SLE. Exercise capacity test may then serve as an important non-invasive prognostic parameter in SSc. In contrast, in SLE prognostic value of CPX would be probably of lesser clinical importance as its abnormal values seem to be rare in this entity. JRCD 2013; 1 (3): 96–102

**Key words:** systemic sclerosis, systemic lupus erythematosus, echocardiography, exercise capacity, cardiopulmonary exercise test

Conflict of interest: none declared.

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## Background

Exercise capacity has been demonstrated to be an independent predictor of mortality in the general population [1]. The data from the literature concentrate mainly on exercise testing in prevalently male patients with coronary artery disease and heart failure. This complicates any extrapolation to autoimmune diseases, characterized by different pathogenesis and affecting predominantly females.

Systemic sclerosis (SSc) is a multisystem disorder characterised by excessive accumulation of collagen and fibrotic tissue in many organs, including the heart [2]. Heart and pulmonary involvement strongly influences prognosis by shortening the survival of SSc patients [3,4]. Systemic lupus erythematosus (SLE) is a generalized autoimmune disease in which diffuse, chronic inflammatory reaction plays an important pathogenic role. Presently, mortality of SLE patients depends mainly on increased occurrence of severe cardio-vascular complications, including heart failure [5].

Conventional risk factors of coronary artery disease (diabetes, hypertension, tobacco use, hyperlipidaemia, sedentary lifestyle) do not explain the increased risk of cardiovascular complications and in consequence of heart failure in SSc and SLE patients [6]. While accumulation of collagen with resulting extensive fibrosis may explain diastolic heart dysfunction and restrictive ventilatory disturbances in SSc patients [7], any possible factors that may influence cardiovascular mortality in SLE are not well understood. Several studies suggest the role of vitamin D: its lower level in SLE may affect the activity of disease and influence cardiovascular complications [8,9].Chronic inflammation may be one of such factors as relation between increased levels of C-reactive protein and life-threatening cardio-vascular episodes has been well-documented [6]. Beside chronic inflammation, another factor that may potentially influence pathologic changes in the arteries is the presence of antiphospholipid antibodies with their pro-thrombotic effects in circulation [10,11].

Unfavorable clinical outcome associated with decreased exercise capacity of the patients has stimulated investigations on the utility of outcome measures appropriate for clinical trials and prognosis evaluation. Presently, a 6-minute walk test and cardiopulmonary exercise test (CPX) are used to assess severity of the impairment of cardiopulmonary function.

The aim of the study was to assess exercise capacity in patients with SSc and SLE by cardiopulmonary exercise test.

## Materials and methods

Three groups of individuals were examined: 46 SSc patients, 60 SLE patients and 30 healthy controls. In the SSc group 25 (54,3%) patients were diagnosed with limited form of SSc, and remaining 21 (45,7%) with its diffuse form. Patients from the SLE group fulfilled at least 4 ACR classification criteria for SLE [12,13]. All the patients examined were in stable clinical conditions (no need for therapy intensification, i.e. current drug dose increase or introduction of an additional drug within last 3 months). In the control group there were no pathologic findings on physical examination; blood pressure and ECG recordings were normal.

In all the patients and controls echocardiography and CPX tests were performed.

The data obtained form echocardiographic examination (Toshiba Aplio SSA-770 Ultrasound System, Toshiba, Japan) included diastolic and systolic dimension of the left ventricle, ejection fraction of left ventricle (Simpson method), thickness of left ventricle walls in diastole, E and A mitral inflow velocity, left atrium and ascending aorta diameters, valvular pressures gradients, regurgitation assessment and right ventricle systolic pressure (RVSP) estimation.

Cardiopulmonary treadmill exercise tests (Marquette Series 2000 Case 16 Treadmill, GE Marquette, USA) were performed using modified Bruce protocol. During the tests ECG, blood pressure, clinical symptoms and time of exercise were recorded. Monitored parameters included: minute ventilation (VE), oxygen uptake (VO2, l/min and ml/kg/min) and carbon dioxide output (VCO2, l/min and ml/kg/min). Based on these, other variables were calculated: oxygen pulse (O2 pulse, 100 ml/beat/kg), ventilation/oxygen uptake ratio slope (VE/VO2) and ventilation/carbon dioxide output ratio slope (VE/VCO2). The VE/VO2 and VE/VCO2 slopes were obtained by linear regression analysis of the data acquired throughout the entire period of exercise (Figure 1) [14].

Statistical analysis was performed using Statistica Six Sigma software. All numerical data were expressed as mean values ± standard deviations or as proportions. Continuous variables were compared by use of t-test. Chi-square test was used to examine differences in proportions. The level for statistical significance was predetermined at $p < 0,05$.

Before the study 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 local ethic committee.

## Results

SSc group consisted of 43 (93,5%) females and 3 (6,5%) males aged 24–73 (mean age 55,4 years). The duration of the disease at the time of examination was 2–32 years (mean 15,5 years). Scl-70 autoantibodies were found in 32 (69,6%) patients, anti-centromere in 12 (26,1%) and other types in 10 (21,7%; anti-fibrillarin, Ku, Ro, antimitochondrial). Physical examination revealed arterial hypertension in 3 patents. There were no complains of dyspnea at rest. Results of peripheral blood count, serum levels of sodium, potassium, glucose, creatinine and urinalysis were all within the normal ranges. The patients were treated with (n; %): pentoxyfilline (32; 69,6%), calcium blockers (14; 30%), cinnarizine (8; 17,4%), nicergoline (5; 10,9%), sadamine (8; 17,4%), bencyclane (5; 10,9%), prednisone (6; 13%), angiotensin converting enzyme inhibitors (14; 30,4%), diosmine (10; 21,7%), ranitidine (6; 13%), hydroxizine (10; 21,7%).

In the SLE group 54 (90%) were females and 6 (10%) males, aged 20–73 years (mean age 51,8 years). The duration of the disease at the time of examination was between 2 and 32 years (mean 15,5 years). Three patients were previously diagnosed with antiphospholipid syndrome (APS) based on the revised APS classifica-

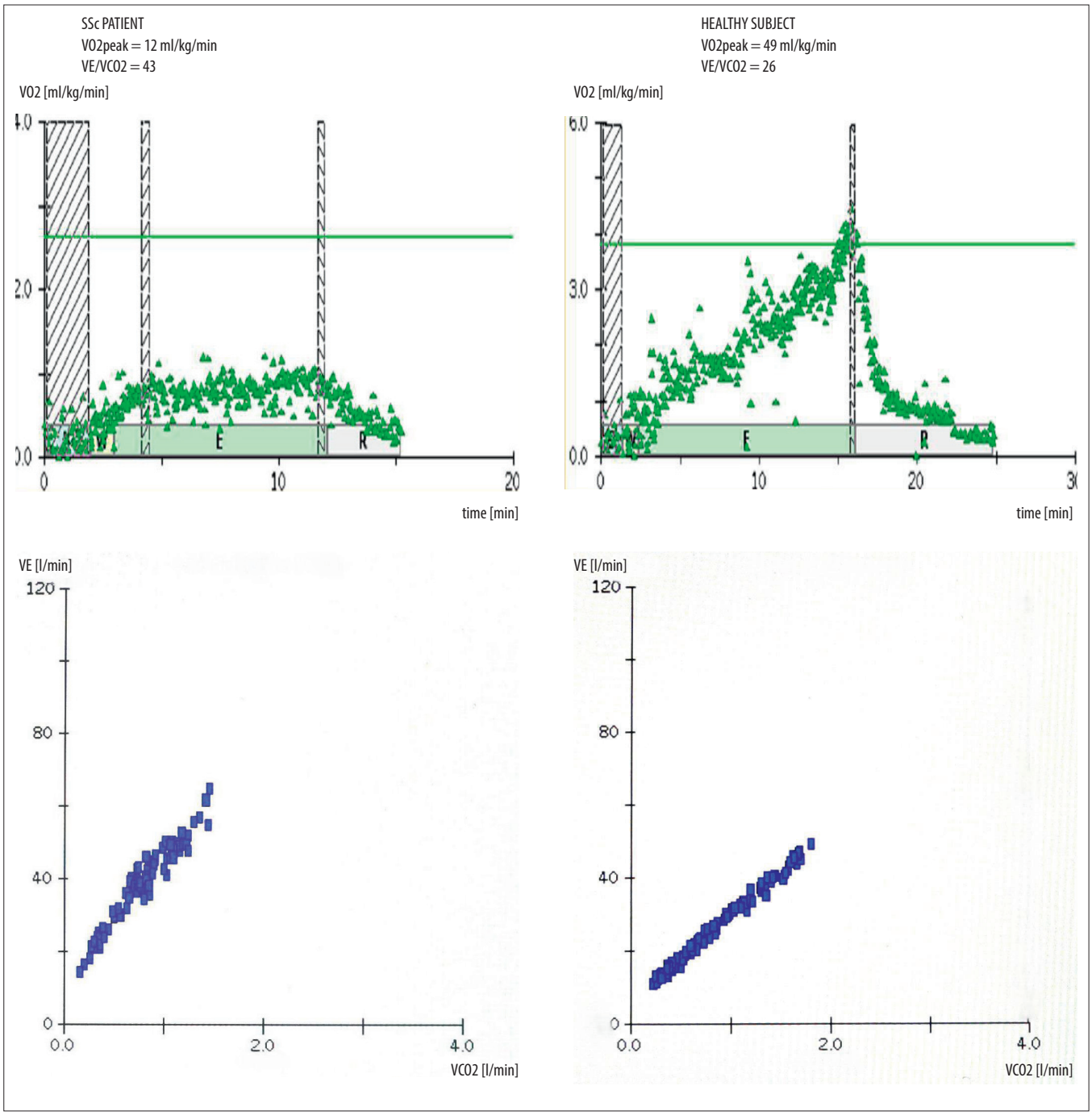


**Figure 1.** Examples of oxygen uptake and ventilation/carbon dioxide output ratio recordings in a systemic sclerosis patient and a healthy subject. SSc – systemic sclerosis, VO2 – oxygen uptake, VCO2 – carbon dioxide output, VE/VCO2 – ventilation/carbon dioxide output ratio, VE – minute ventilation

tion criteria [13]. One of these three suffered from an objectively confirmed pulmonary embolism. There were 2 tobacco smokers, none of the patients was obese. History revealed arterial hypertension in 3 subjects. ECG recordings were normal in all the patients. The results of peripheral blood count, serum sodium, potassium, glucose, creatinine and urinalysis were all normal. The SLEDAI score in all patients [14] ranged from 0 to 20 (median 4), but in 55 of them (91,7%) ranged from 2 to 8. Main laboratory abnormalities at inclusion were related to autoimmunization: low C3c and C4 complement components in 32 (53,3%) patients, elevated levels of antiphospholipid antibodies in 26 (43,3%) and the presence of antinuclear antibodies in 56 (93,3%). Immunosuppressive treatment included: methylprednisolone in 32 (53,3%) subjects, prednisone in 2 (3,3%), chloroquine derivate in 5 (8,3%), azathioprine in 4 (6,7%), cyclophosphamide in 3 (5%), methotrexate in 2 (3,3%). Remaining 12 (20%) patients did not use any immunosuppressive drugs in

the last 12 months. Other treatment included angiotensin converting enzyme inhibitors in 4 (6,7%) subjects, beta blockers in 3 (5%) and calcium channel blockers in 2 (3,3%).

Control group included females aged 38 – 57 (mean age 51,6 years).

Echocardiography showed normal left ventricle systolic function in all patients. Mean value of the left ventricle ejection fraction in the patients did not differ from the controls (Table 1). Left ventricle end-diastolic diameter was increased (>56mm) in 2 (3,3%) SLE patients. In contrast, mitral inflow E/A ratio showed significant diastolic left ventricular dysfunction in all of SSc patients; in 5 patients pseudonormal inflow pattern was observed, indicating advanced diastolic dysfunction, in other 41 patients (89,1%) significantly decreased E/A ratio reflecting relaxation impairment was shown (Table 1). In SLE group decreased E/A ratio was observed in 13 (21,7%) patients. Diastolic left ventricular dysfunction was present despite normal left ventricle muscle thickness: interventricular septum or posterior wall hypertrophy (>12 mm) was present in only 2 (4,3%) SSc and 2 (3,3%) SLE patients.

In spite of the lack of clinically significant valvular stenosis in our patients, mitral and aortic leaflet thickening was observed frequently, especially in SLE group, where more than 60% of patients revealed changes visible by standard echocardiography (Table 1). Pericardial thickening was also frequent in this group, with pericardial effusion (2–12 mm) present in 43,3% of the patients (Table 1). Clinically relevant mitral regurgitation ($^3$2nd degree) was present in 1 SLE patient. Left ventricle diastolic dysfunction resulted in a dilation of the left atrium in 11 (18,3%) SSc and in 6 (10%) SLE patients. There was no aortic dilation in any of the patients nor in the control group.

Right ventricle systolic pressures were elevated (>30 mmHg) in 14 (30,4%) SSc and in 10 (16,7%) SLE patients. In spite of the frequent RVSP elevation in SSc group, right ventricle dilation (>30 mm in parasternal view) was present in only 3 (21,4%) of them. On the contrary, right ventricle was dilated in all SLE patients with RVSP elevation.

During cardiopulmonary exercise tests the patients exercised above their anaerobic threshold and achieved a high peak respiratory exchange ratio (RER = VCO2/VO2), that is $^3$ 1,05 in all groups, suggesting that they developed significant metabolic acidosis and exercised close to maximal intensity. CPX tests showed low exercise capacity predominantly in SSc patients. The time of exercise was significantly shorter as compared to control subjects (Table 2). The main finding, however, was a severe decrease in peak oxygen uptake (VO2peak) and low carbon dioxide output (VCO2peak) in SSc group (Table 2). The ratios of ventilation/oxygen uptake (VE/VO2) and ventilation/carbon dioxide output (VE/VCO2) were markedly increased in SSc patients, who maintained higher ventilation to consume the same amount of oxygen and to exhale the same amount of carbon dioxide than the control subjects. While the increase of VE/VCO2 above 34, that is the prognostic cut-off point for heart failure subjects [17], was present in 69,6% of SSc patients, it was increased in only 6,7% of the SLE group (Table 3). Mean values of gas exchange parameters did not differ between SLE and control groups (Table 2). Examples of VO2 and VE/VCO2 recordings during exercise in a SSc patient and in a healthy subject from control group are shown in Figure 1.

VO2peak is widely used to classify patients according to the level of cardiopulmonary failure due to Weber criteria [18]. Healthy subjects or mild failure patients (class A) are characterized by VO2peak > 20 ml/kg/min, moderate failure (class B) by VO-2peak = 16–20 ml/kg/min, severe failure (class C) by VO2peak = 10–15 ml/kg/min, while end-stage failure (class D) by VO2peak < 10ml/kg/min. In our study VO2peak was higher than 20 ml/kg/min in all the subjects from control group. Weber class C or D was

**Table 1. Echocardiographic data of SSc and SLE patients and of control subjects**

| | SSc n = 60 | SLE n = 60 | controls n = 30 | p* |
|---|---|---|---|---|
| LVEDD [mm] | 47,7 ±5,9 | 45,4 ±4,8 | 46,9 ±3,9 | ns |
| LVESD [mm] | 30,5 ±7,5 | 31,4 ±4,8 | 28,4 ±3,3 | ns |
| LVEF [%] | 67,4 ±9,4 | 64,6 ±3,9 | 65,8 ±6,1 | ns |
| E/A mitral | **0,87 ±0,2** | 1,29 ±0,4 | 1,38 ±0,5 | **0,001** |
| IVS thickness [mm] | 9,2 ±1,7 | 8,9 ±1,3 | 9,0 ±1,9 | ns |
| PW thickness [mm] | 9,3 ±1,4 | 8,7 ±1,3 | 8,3 ±1,5 | ns |
| mitral leaflets thickening [n,%] | **14 (30,4%)** | **36 (60%)** | 0 | **0,01** |
| aortic leaflets thickening [n,%] | 17 (37,0%) | **38 (63,3%)** | 0 | **0,01** |
| pericardium thickening [n,%] | **6 (13,0%)** | **36 (60%)** | 0 | **0,01** |
| pericardial effusion [n,%] | **8 (13,0%)** | **16 (43,3%)** | 0 | **0,01** |

LVEDD – left ventricle end-diastolic diameter, LVESD – left ventricle end-systolic diameter, LVEF – left ventricle ejection fraction, E/A mitral – ratio of early (E) to late (A) mitral inflow velocity, IVS – interventricular septum, PW – posterior wall, SSc – systemic sclerosis, SLE – systemic lupus erythematosus
* p value for the difference between patient groups (bold letters) and controls

**Table 2. Cardiopulmonary exercise test results in SSc and SLE patients and in control subjects**

| | SSc patients (n = 46) | SLE patients (n = 60) | control group (n = 30) | p* |
|---|---|---|---|---|
| exercise time [min] | **13,1 ± 4,8** | 15,6 ± 4,0 | 17,8 ± 2,6 | **0,01** |
| HR peak [/min] | 142,6 ± 21,7 | 148,0 ± 23,9 | 166,3 ± 17,3 | ns |
| SBP peak [mmHg] | 165,5 ± 36,4 | 140,7 ± 29,7 | 155,0 ± 32,5 | ns |
| DBP peak [mmHg] | 84,5 ± 13,8 | 74,4 ± 10,8 | 85,0 ± 11,5 | ns |
| VO2 peak [l/min] | **1,04 ± 0,40** | 1,70 ± 0,51 | 1,70 ± 0,43 | **0,0001** |
| VO2 peak [ml/kg/min] | **16,51 ± 6,86** | 26,3 ± 7,08 | 25,66 ± 6,62 | **0,001** |
| O2 pulse [100ml/b/kg] | **8,76 ± 2,16** | 17,6 ± 4,22 | 11,5 ± 1,88 | **0,001** |
| VCO2 peak [l/min] | **1,04 ± 0,47** | 1,66 ± 0,61 | 1,73 ± 0,44 | **0,0004** |
| VCO2 peak [ml/kg/min] | **16,59 ± 7,09** | 25,85 ± 6,90 | 27,33 ± 6,71 | **0,0004** |
| VE/VO2 | **37,5 ± 8,1** | 26,0 ± 4,2 | 27,4 ± 4,6 | **0,01** |
| VE/VCO2 | **38,7 ± 7,5** | 26,8 ± 4,5 | 25,6 ± 4,2 | **0,01** |

HR – heart rate, SBP (DBP) – systolic (diastolic) blood pressure, VO2 – oxygen uptake, O2 pulse – oxygen uptake for 1 heart beat, VCO2 – carbon dioxide output, VE – minute ventilation, SSc – systemic sclerosis, SLE – systemic lupus erythematosus
* p value for the difference between patient groups (bold letters) and controls

**Table 3. Number of SSc and SLE patients and of healthy subjects with decreased peak oxygen uptake and increased ventilation/carbon dioxide output ratio**

| | SSc patients (n = 46) | SLE patients (n = 60) | control group (n = 30) | p* |
|---|---|---|---|---|
| VO2 peak (< 20 ml/kg/min) | **36 (78,3%)** | **13 (21,7%)** | 0 (0%) | **0,01*** **0,05**** |
| VE/VCO2 (> 34) | **32 (69,6%)** | 4 (6,7%) | 0 (0%) | **0,01*** |

SSc – systemic sclerosis, SLE – systemic lupus erythematosus, VO2 peak – peak oxygen uptake, VE/VCO2 – ventilation / carbon dioxide output ratio
* p value for the difference between SSc patients and controls
** p value for the difference between SLE patients and controls

observed in 20 (43,5%) SSc patients, but in only in 2 (3,4%) SLE patients (Figure 2).

## Discussion

Cardiopulmonary exercise testing has become an important clinical tool to evaluate functional capacity and to predict outcomes in patients with systolic [19] and diastolic [20] heart failure. CPX-derived measures of oxygen uptake at peak exercise (VO2peak) has been shown to be a major prognostic marker in patients with systolic heart failure [21]. More recently, slope of the ventilation to CO2 production ratio (VE/VCO2) has been proposed as a valuable prognostic tool also in patients with diastolic heart failure [20,22].

Diastolic left ventricle failure was the main echocardiographic finding in our SSc patients. Heart involvement in systemic sclerosis results from fibroblast proliferation and overproduction of collagen [2] and is related to poor prognosis [3,4]. In our study systolic left ventricle function was normal in all patients and comparable to healthy controls. This normal systolic function despite pathologic changes in the myocardium may be partially explained by adrenergic overactivity in systemic sclerosis, manifested by commonly observed tachycardia [23]. In SSc myocardial ischemia 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 otherwise well-perfused myocardium [24]. While diastolic dysfunction results mainly from myocardial fibrosis [2], important role of myocardial ischaemia should also be emphasized. Diastolic function of myocardium is very sensitive to

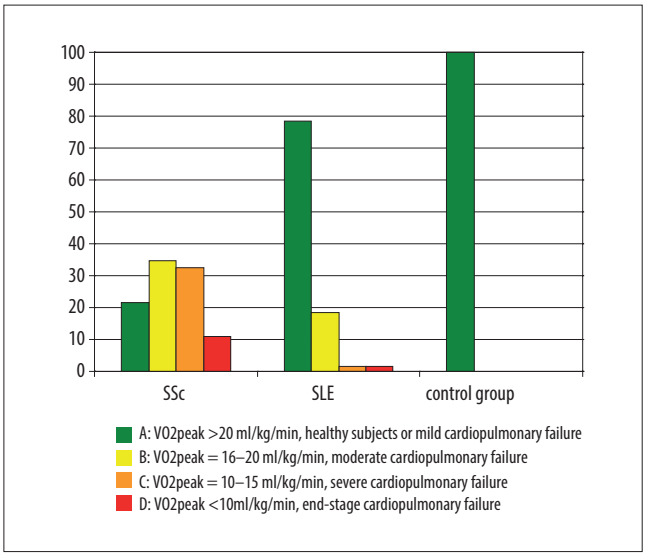


**Figure 2.** Distribution of systemic sclerosis and systemic lupus erythematosus patients and of control subjects according to Weber classification of cardiopulmonary failure. VO2 – oxygen uptake, SSc – systemic sclerosis, SLE – systemic lupus erytmetosus

ischaemia [25]. Even small regions of low-perfused myocardium may aggravate diastolic dysfunction resulting from fibrosis. Of note, diastolic dysfunction had been present despite normal left ventricle wall thickness, and was not related to muscle hypertrophy.

Beside heart involvement, pulmonary pathology represents a second factor influencing patients prognosis [2]. As previously reported, mild pulmonary hypertension was present in 30% of SSc patients [26,27].

While collagen overproduction in SSc results in the significant diastolic left ventricle dysfunction, generalized inflammation in SLE leads mainly to pathologic thickening of valvular leaflets and/or pericardium. Systolic function of left ventricle in our SLE patients was normal, with mild diastolic dysfunction present in 21,7% of the patients. Pulmonary hypertension was also less frequent in SLE, with RVSP > 30 mmHg in 16,7% of them.

CPX tests showed exercise capacity impairment in SSc group, as manifested by a shorter time of exercise, significantly decreased VO2peak and significantly increased VE/VCO2.

VO2peak is influenced by several factors: oxygen-carrying capacity of the blood, cardiac function, regional and local distribution of peripheral blood flow and extraction by the tissues [14]. It is generally accepted that VO2peak < 10 ml/kg/min is always associated with a very poor prognosis, while VO2peak > 18 ml/kg/min is related to a good outcome [28]. In our study VO2peak was £ 15ml/kg/min in 43,5% of SSc patients and only in 3,4% of SLE patients. These results may indicate very poor prognosis for a large group of SSc subjects. In a study of 116 candidates for cardiac transplantation, VO2peak £ 14 ml/kg/min was related to a high mortality or urgent cardiac transplantation at 1 year (48%), while VO2peak > 14 ml/kg/min predicted a 1-year survival of 94% [21]. Diminished exercise capacity with low VO2peak in SSc has been already reported [26,29,30]. A recent report examining VO2peak in 46 SSc patients [31] suggested that CPX should be included among the battery of standard tests used to determine severity of SSc. Reduced VO2peak was described also in SSc patients without pulmonary impairment [29], suggesting that left ventricle diastolic dysfunction plays the key role in exercise intolerance in the majority of these patients.

Diastolic left ventricle dysfunction in SSc patients is also related to VE/VCO2. It has been suggested as a valuable prognostic tool in patients with diastolic heart failure [20,22]. Elevation of VE/VCO2 in heart failure is mainly due to VE increase caused by enlarged death space with ineffective ventilation, leading to early occurrence of lactate acidosis and disturbed activation of chemoreceptors and metaboreceptors [14,32–34]. In the recent study conducted to compare exercise capacity in patients with systolic and diastolic heart failure [20], VE/VCO2 ratios were abnormal and comparable in both groups. However, a large prospective study showed that after multivariate analysis VE/VCO2 remained the only predictor of total mortality and hospitalizations in diastolic heart failure patients [22]. Interestingly, in this study as in other previous studies with congestive heart failure patients and in our study with autoimmune disease-related heart failure patients, the values of VE/VCO2 in subjects with diastolic heart failure were similar (37,0 ±12,0 [35], 33,2 ±7,9 [36], 34,0 ±8,0 [37], 38,7 ±7,5 in our study). This might suggest that an impairment in ventilatory efficiency could be used for the estimation of risk among patients with heart failure, and that this risk is equally powerful for any patient with diastolic heart failure regardless of its pathogenesis. It should be emphasized that prognosis of patients suffering from diastolic heart failure is as ominous as in those suffering of systolic heart failure [38,39].

The results discussed above may have important implications for the treatment of SSc patients. Detection of a severe heart failure with resultant poor prognosis caused predominantly by diastolic left ventricle dysfunction should stimulate efforts to limit (if possible) fibrosis progression. In this context potential beneficial effect of angiotensin converting enzyme inhibitors on diastolic function of the left ventricle in SSc patients should be mentioned [40,41].

## Conclusion

Overproduction of collagen in SSc results in diastolic left ventricle dysfunction. On the other hand, generalized inflammation in SLE leads mainly to pathologic changes on valvular leaflets and/or pericardium. While exercise intolerance expressed by VO2peak < 15 ml/kg/min and VE/VCO2 > 34 is present in 50% of SSc patients, gas exchange parameters in majority of SLE patients remained unchanged. Prognostic value of this difference in exercise capacity between SSc and SLE patients should be examined in further clinical trials.

## References

1. Ekelund LG, Haskell WL, Johnson JL, et al.: Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. N Engl J Med 1998; 319: 1379–1384.
2 Braun-Falco O, Plewig G, Wolff HH: Diseases of Connective Tissue, Systemic Sclerosis. In: *Dermatology*. Edited by Braun-Falco O. Berlin: Springer-Verlag; 2000: 789.

3. Kostis JB, Seibold JR, Turkevich D, Masi AT, Gran RG, Medsger TA et al.: Prognostic importance of cardiac arrhythmias in systemic sclerosis. *Am J Med* 1988; 84: 1007–1017.
4. Wynn J, Fineberg N, Matzer L, Cortada X, Armstrong W, Dillon JC, Kinney EL: Prediction of survival in progressive systemic sclerosis by multivariate analysis of clinical features. *Am Heart J* 1985; 110: 123–127.
5. Bruce IN: "Not only… but also": factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology 2005; 44: 1492–1502.
6. Pons-Estel GJ, Gonzales LA, Zhang J, Burgos PI, Reveille JD, Villa LM, Alarcon GS: Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multicenter US cohort. Rheumatology 2009; 48: 817–822.
7. Plazak W, Zabinska-Plazak E, Wojas-Pelc A, Podolec P, Olszowska M, Tracz W, Bogdaszewska-Czabanowska J: Heart structure and function in systemic sclerosis. *Eur J Dermatol* 2002; 12: 257–262.
8. Perricone C, Agmon-Levin N, Colafrancesco S, Shoenfeld Y: Vitamins and systemic lupus erythematosus: to D or not to D. *Expert Rev Clin Immunol* 2013; 9(5): 397–9.
9. Tamez H, Zoccali C, Packham D, Wenger J, Bhan I, Appelbaum E, Pritchett Y, Chang Y, Agarwal R, Wanner C, Lloyd-Jones D, Cannata J, Thompson BT, Andress D, Zhang W, Singh B, Zehnder D, Pachika A, Manning WJ, Shah A, Solomon SD, Thadhani R: Vitamin D reduces left atrial volume in patients with left ventricular hypertrophy and chronic kidney disease. *Am Heart J* 2012; 164(6): 902–9.
10. Pierangeli SS, Espinola RG, Liu XW, Harris EN: Thrombogenic effect of antiphospholipid antibodies are mediated by intracellular adhesion molecule-1, vascular cell adhesion molecule-1 and P-selectin. Circ Res 2001; 88: 245–250.
11. Campbell AL, Pierangeli SS, Wellhausen S, Harris EN: Comparison of the effect of anticardiolipin antibodies from patients with antiphospholipid syndrome and with syphilis on platelet activation and aggregation. Thromb Heamost 1995; 73: 519–524.
12. Smolen J, Weisman M: Connective tissue disorders. In: *Rheumatology*. Edited by Hochberg M, Silman A, Smolen J, Weinblatt M, Weisman M. Philadelphia: Mosby Elsevier; 2008: 1205–485.
13. Smith EL, Shmerling RH: The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: strengths, weaknesses, and opportunities for improvement. *Lupus* 1999; 8, 586–595.
14. Task Force of the Italian Working Group on Cardiac Rehabilitation and Prevention endorsed by the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology: Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricle dysfunction: recommendations for performance and interpretation. Part I: Definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prevention Rehabilitation* 2006; 13: 150–164.
15. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al.: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Heamost* 2006; 4: 295–306.
16. Permarheum SLEDAI Calculator: www.permarheum.org/SLEDAI.html
17. Arena R, Myers J, Guazzi M: The clinical and research application of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev* 2008; 13: 245–269.
18. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP: Oxygen utilization and ventilation during exercise in patients with chronic heart failure. Circulation 1982; 65: 1213–1223.
19. Beniaminovitz A, Mancini DM: The role of exercise-based prognosticating algorithms in the selection of patients for heart transplantation. *Curr Opin Cardiol* 1999; 14: 114–120.
20. Farr MJ, Lang CC, LaManca JJ, Zile MR, Francis G, Tavazzi R et al.: Cardiopulmonary exercise variables in diastolic versus systolic heart failure. *Am J Cardiol* 2008; 102: 203–206.
21. Mancini D, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR: Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83: 778–786.
22. Guazzi M, Myers J, Arena R: Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005; 46: 1883–1890.
23. Ferri C, Emdin M, Giuggioli D, Carpeggiani C, Maielli M, Varga A et al.: Autonomic dysfunction in systemic sclerosis: time and frequency domain 24 hour heart rate variability analysis. *Br J Rheumatol* 1997; 36: 669–676.
24. Gurtner C, Werner RJ, Winten G, Krause BJ, Wendt T, Hor G, Holzmann H: Early diagnosis of cardiac involvement systemic sclerosis by 123I-MIBG neurotransmitter scintigraphy. *Nucl Med Commun* 1998; 19: 849–857.
25. Garcia-Fernandez MA, Azevedo J, Moreno M, Bermejo J, Perez-Castellano N, Puerta P et al.: Regional diastolic function in ischemic heart disease using pulsed wave Doppler tissue imaging. *Eur Heart J* 1999; 20: 496–505.
26. Morelli S, Ferrante L, Sgreccia A, Eleuteri ML, Perrone C, DeMarzio P, Balsano F: Pulmonary hypertension is associated with impaired exercise performance in patients with systemic sclerosis. *Scand J Rheumatol* 2000; 29: 236–242.
27. Morelli S, Barbieri C, Sgreccia A, Ferrante L, Pittoni V, Conti F et al.: Relationship between cutaneous and pulmonary involvement in systemic sclerosis. *J Rheumatol* 1997; 24: 81–85.
28. Task Force of the Italian Working Group on Cardiac Rehabilitation and Prevention endorsed by the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology: Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricle dysfunction: recommendations for performance and interpretation. Part III: Interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications. *Eur J Cardiovasc Prevention Rehabilitation* 2006; 13: 485–494.
29. de Oliveira NC, dos Santos Sabbag LM, Ueno LM, de Souza RB, Borges CL, de Sa Pinto AL, Lima FR: Reduced exercise capacity in systemic sclerosis patients without pulmonary involvement. *Scand J Rheumatol* 2007; 36: 458–461.
30. Sudduth CD, Strange C, Cook WR, Miller KS, Baumann M, Collop NA, Silver RM: Failure of the circulatory system limits exercise performance in patients with systemic sclerosis. *Am J Med* 1993; 95: 413–418.
31. Cuomo G, Santoriello C, Polverino F, Ruocco L, Valentini G, Polverino M: Impaired exercise performance in systemic sclerosis and its clinical correlations. Scand J Rheumatol, 2010; 39: 330–335.
32. Uren NG, Davies SW, Agnew JE, Irwin AG, Jordan SL, Hilson AJ, Lipkin DP: Reduction of mismatch of global ventilation and perfusion on exercise is related to exercise capacity in chronic heart failure. *Br Heart J* 1993; 70: 241–246.
33. Chua TP, Clark AI, Amadi AA, Coats AJ: Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1996; 27: 650–657.
34. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH et al.: Enhanced ventilatory response in patients with heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001; 103: 967–972.
35. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, Coats AJ: Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO2 slope and peak VO2. *Eur Heart J* 2000; 21: 154–161.
36. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA: Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; 147: 354–360.
37. Guazzi M, Reina G, Tumminello G, Guazzi MD: Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO2 partial pressure. *Eur Heart J* 2005; 26: 472–480.
38. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC, ADHERE Scientific Advisory Committee and Investigators: Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function. *J Am Coll Cardiol* 2006; 47: 76–84.
39. Aurigemma P: Diastolic heart failure – a common and lethal condition by any name. *N Engl J Med* 2006; 355: 308–310.
40. Sun Y, Zhang JQ, Zhang J, Ramires FJ: Angiotensin II, transforming growth factor b1 and repair in the infarcted heart. *J Mol Cell Cardiol* 1998; 30: 1559–1569.
41. Brilla CG, Janicki JS, Weber KT: Cardioreperative effects of lisinopril in rats with genetic hypertension and left ventricular hypertrophy. Circulation 1991; 83, 1771–1779.