High-intensity interval training can improve hand grip strength, inspiratory muscle, and quality of life in systemic sclerosis subjects

Irma Ruslina Defi, Chandrawati Gultom, Maria Jessica Chorman, Jennie Jennie

1Department of Physical Medicine and Rehabilitation, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
2Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia

Abstract

Introduction: Systemic sclerosis/scleroderma (SSc) is a chronic autoimmune disease with connective tissue, multi-organ, and multisystem involvement. The disease has three main characteristics, namely vasculopathy, fibrosis, and autoimmunity. The effect of high-intensity interval training (HIIT) in aerobic exercise on other rheumatic diseases has been studied, for example in patients with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). The purpose of this work is to investigate the effectiveness of HIIT of aerobics exercise on improving the inspiratory muscle, quality of life and functional ability for systemic sclerosis subjects.

Material and methods: The study was conducted on patients with confirmed systemic sclerosis who met the inclusion criteria. The research was carried out for 12 months in the outpatient clinic and gait laboratory of the Department of Physical Medicine and Rehabilitation.

Results: After HIIT in aerobic exercise, we found significant changes in inspiratory muscle (SNIP values 45.67 [30.92] vs. 54.25 [22.71]), handgrip (13.14 [4.42] vs. 15.63 [4.08]), walking speed (184.70 [26.86] vs. 246.6 [12.30]), metabolic equivalent (3.53 [0.30] vs. 4.21 [1.25]) and Scleroderma-Specific Health Assessment Questionnaire Disability Index for all visual analog scale (VAS) domains except Disability Index. Exercise approaches are characterized by repeated cycles of exercise interrupted by rest. For a range of clinical conditions, HIIT in aerobic exercise is known to remedy blood vessel function.

Conclusions: Our results suggest that HIIT in aerobic exercise has improved functional ability, respiratory muscle strength, and quality of life in SSc subjects. Training twice a week in a 12-week HIIT program is considered to be safe for this population. We have to consider internal and external factors that influenced the result. A larger sample and further exploration of the feasibility of combined exercise in SSc patients should be the focus for future research.

Key words: aerobic exercise, highintensity interval training, rehabilitation, systemic sclerosis.

Introduction

Systemic sclerosis (SSc) is an connective tissue disease with three main characteristics, namely vasculopathy, fibrosis, and autoimmunity. Considering the pattern of skin involvement, clinical manifestations and laboratory results, SSc is divided into two main classifications, namely diffuse cutaneous SSc (dcSSc) and limited cutaneous sclerosis (lcSSc). The type most often encountered is diffuse cutaneous SSc, which is associated with hardening of the skin in the proximal part of the body (trunk, arms, and/or upper limbs), interstitial lung disease (ILD), which is a thickening of the interstitium due to inflammation or autoimmunity, and cardiac fibrosis. Patients with lcSSc are identified with hardening of the skin on the distal extremities and head. The prognosis of lcSSc is said to be better than that of dcSSc [1, 2].
Every year the incidence of SSC is 4–43 individuals/million population, with prevalence of 70–340 cases/million population. Women have more systemic sclerosis with a ratio of 6:1 [3]. According to data obtained at our hospital in 2017, connective tissue disease was the most common disease in 2014 and 2015 in the Rheumatology Department.

Systemic sclerosis is the third most common disease in the Rheumatology Clinic of our hospital, with the number of cases increasing from 189 patients/year in 2014 to 196 patients/year in 2015 [4].

Although the cutaneous implication is the most proven, the disease can affect multiple organs and systems, which can worsen the prognosis, such as the lung, the heart, the kidneys, the musculoskeletal system and the gastrointestinal tract [5].

In systemic sclerosis/scleroderma, joint deformities cause the limitation of movement and consequent restricted mobility, which can reduce functional capacity and quality of life can be affected directly for these patients [6].

Subjects with SSc generally experience a decrease in physical fitness where SSC has a decreased average training capacity compared to healthy individuals and the general population. The aerobic functional capacity of SSC patients can decrease even without the involvement of the pulmonary and cardiac processes.

This decrease can occur due to inactivity, the influence of drugs that cause muscle weakness, and impaired oxygen diffusion due to undetected early phase pulmonary fibrosis. The underlying pathogenesis is decreased aerobic capacity, which causes fatigue and is closely related to decreased quality of life [7].

Research showed that SSC patients have good exercise tolerance and moderate-intensity aerobic exercise can increase aerobic capacity and muscle strength, and improve hand mobility, function in daily activities, and quality of life (HRQoL), even in SSC patients with lung involvement [8].

Mitropoulos et al. [9] tested the effect of high-intensity interval training (HIIT) in aerobic exercise in patients with SSC. The results of this study concluded that HIIT involving the upper limbs might improve microvascular reactivity by improving endothelial function, thereby reducing the risk of finger ischemia. Less ischemia will reduce pain and improve the quality of life. HIIT is a non-invasive program and can be an adjunct to pharmacological management to reduce Raynaud’s phenomenon in SSC [9].

To the best of our knowledge, the subject of HIIT in aerobic exercise and its effect on respiratory muscle strength is not thoroughly investigated. The study aims to elucidate the effect of high-intensity interval aerobic exercise on respiratory muscle strength, functional ability, and quality of life.

Material and methods

This study used a quasi-experimental, pre-post design. The subjects were patients with SSC who had routine treatment at the rheumatology clinic at our hospital, who met the inclusion criteria. The research was conducted in the gym of the outpatient clinic and gait laboratory of the Department of Physical Medicine and Rehabilitation between April 2019 and April 2020. Respiratory muscle strength (RMS) was taken from the result using a micro respiratory pressure meter (RPM). Functional ability can be represented by handgrip strength, walking speed, and metabolic equivalent (METs). Quality of life was measured by the SHAQ-DI questionnaire [10].

Inclusion criteria were male or female patients 18–59 years old, diagnosed with SSC based on the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) criteria [11], who had had the disease for 1 to 10 years. All participants were able to carry out the exercise.

Patients who were excluded were those with ILD, those diagnosed with another inflammatory condition and/or presenting myositis with proximal muscle weakness, and pulmonary arterial hypertension. Moreover, patients with a Mini-Mental State Examination (MMSE) score < 24, New York Heart Association class 3 or 4, pregnant women, and smokers or people who stopped smoking within 4 weeks of screening also could not participate.

Respiratory muscle strength was represented by inspiratory muscle strength and measured from sniff nasal inspiratory pressure (SNIP). The SNIP was used to more easily assess inspiratory muscle function as a non-invasive test. The SNIP measurement entails brief maximal sniff efforts by the patient during simultaneous intranasal pressure recordings within a nostril that is sealed by a snugly fitting plug containing the pressure-sensing probe.

To insert the nasal probe and to ensure the appropriate size of the nasal probe to prevent air leakage during sniffing, verified clinically, the nostril which looked most patent was selected. The patient was asked to perform, without a prior training period, short sharp inhalations with a maximum intensity of functional residual capacity (FRC) in a sitting position with the mouth closed and the contralateral nostril closed. Normal breathing was allowed between experiments [12, 13].

Hand grip strength was evaluated with a hand dynamometer (hydraulic dynamometer, model SH5001, Saehan Corporation, Korea) and following the American Society of Hand Therapists recommendations [14].

Reumatologia 2021; 59/2
Subjects were seated with the arms parallel to the body, flexed at the elbow to 90°, and the forearm in a neutral position. Wrist flexion or extension was not allowed. Each participant’s grip strength was measured for each hand 3 times in each of 5 different handle positions. The position at which they achieved maximal grip strength is the best position for each participant.

Walking speed was assessed through the six-minute walking test (6MWT) [15]. Although the 6MWT lacks organ specificity in SSc, it can be suggested as a regular assessment in this clinical condition and provides a valuable outcome measure. Patients were requested to walk as far back and forth as possible for 6 min over 10 m. They were also instructed if out of breath or exhausted to slow down, stop and/or rest as necessary, but to resume walking as soon as they felt capable. The total walking distance and the laps were recorded on a worksheet, and also we measured for metabolic equivalents (METs).

The Scleroderma-Specific Health Assessment Questionnaire Disability Index (SHAQ_DI) is used to assess the quality of life. The SHAQ-DI combines the disability and pain scales of the Health Assessment Questionnaire (HAQ) with five scleroderma-specific VASs for digital ulcers, Raynaud’s phenomenon, pulmonary symptoms, digestive symptoms, and overall disease severity, with each VAS score scaled from 0 to 3. SSc can be measured with SHAQ for the most extensively used and best-characterized outcome measure. A combined SHAQ score was calculated by pooling the eight HAQ-DI domains and the five VASs [10, 16].

Exercise procedure

Patients took twice-weekly supervised exercise sessions at the Department of Physical Medicine and Rehabilitation, Hasan Sadikin General Hospital for twelve weeks. Each session started with a 5 min warm-up with an arm crank or cycle ergometer depending on the group (involving gentle range of motion exercises and light aerobic exercise). This was followed by HIIT for 30 sec seconds at 100% of peak power output (PPO) interspersed by 30-second passive recovery for a total of 30 min [9].

Qualifying patients were recruited from the Rheumatology Clinic at our hospital. Prior to the study, ethical clearance was obtained from the Profession and Research Ethics Committee of the Medical Committee Faculty of Medicine, Padjadjaran University (ethical clearance number: LB.02.01/X.6.5/142/2019). As required, procedures and ethical aspects of current research have been conducted in full accordance with the World Medical Association Declaration of Helsinki, and all participants gave their written consent for their participation in the current study.

Results

We recruited 11 patients in accordance with the American College of Rheumatology and European League Against Rheumatism criteria. All participants were women and were given an introduction program for 3 days before the study was conducted (Table I). In Table II above, there are no significant differences between before and after exercise. The exercise is safe for SSc patients in our study.

Respiratory muscle strength represented by inspiratory muscle was measured by the SNIP examination (Table III). The value of SNIP was calculated from the average of the 5 sniff trials from the patent nostril with the contralateral nostril closed. The results show a sig-

### Table I. Subjects’ characteristics

| Parameter          | Mean (SD)   |
|--------------------|-------------|
| Age [years]        | 40.91 (13.38)|
| Weight [kg]        | 47.65 (9.73) |
| Height [cm]        | 146.9 (30.57)|
| Education, n (%)   |             |
| Elementary         | 0 (0)       |
| Junior High School | 3 (27.20)   |
| Senior High School | 2 (18.10)   |
| Vocational High School | 2 (18.10) |
| Bachelor           | 4 (36.30)   |

### Table II. Data and vital sign

| Variable                        | Before exercise Mean (SD) | After exercise Mean (SD) | p-value |
|---------------------------------|---------------------------|--------------------------|---------|
| Systolic blood pressure [mm Hg] | 105.30 (11.04)            | 102.50 (7.90)            | 0.8125  |
| Diastolic blood pressure [mm Hg]| 68.09 (7.00)              | 67.00 (9.49)             | 0.5625  |
| Pulse (BPM)                     | 83.91 (12.67)             | 90.10 (11.08)            | 0.1275  |

### Table III. Data of respiratory muscle strength by sniff nasal inspiratory pressure

| Variable | Before exercise Mean (SD) | After exercise Mean (SD) | p-value |
|----------|---------------------------|--------------------------|---------|
| SNIP [cm H2O] |                         |                          |         |
| Mean     | 45.67 (30.92)            | 54.25 (22.71)            | 0.0041* |
| Median   | 33.20                    | 55.45                    |         |
| Range    | 10.70–115.10             | 26.20–82.80              |         |

*The significance value is based on the p-value < 0.05. * sign indicates the p-value < 0.05.*
High-intensity interval training in systemic sclerosis subjects

Reumatologia 2021; 59/2

In Table IV, it can be seen that there is a significant difference in the handgrip strength walking speed and METs variables between before and after exercise in the SSc patients. A walking speed test was carried out by the 6MWT.

The statistical test results showed that there is a significant difference between before and after intervention for the VAS scale in digestive VAS, pulmonary VAS, Raynaud’s VAS, digital ulcers VAS, and overall disease VAS, but not for Disability Index variables (Table V).

### Table IV. Functional ability before and after exercise

| Variable                  | Before exercise Mean (SD) | After exercise Mean (SD) | p-value |
|---------------------------|---------------------------|--------------------------|---------|
| Hand grip strength [lbs.] | 13.14 (4.42)              | 15.63 (4.08)             | 0.0031* |
| Walking speed [m/s]       | 184.70 (26.86)            | 246.60 (12.30)           | 0.0039* |
| METs                     | 3.53 (0.30)               | 4.21 (1.25)              | 0.0039* |

**MET** – metabolic equivalent. The significance value is based on the p-value < 0.05. * sign indicates the p-value < 0.05.

### Table V. Comparison of Scleroderma-Specific Health Assessment Questionnaire Disability Index domain questionnaire

| Variable                  | Before exercise Mean (SD) | After exercise Mean (SD) | p-value |
|---------------------------|---------------------------|--------------------------|---------|
| Disability Index Scale    | 0.64 (0.70)               | 0.36 (0.41)              | 0.0571  |
| Pain VAS                  | 1.40 (0.84)               | 0.98 (0.73)              | 0.0011* |
| Digestive VAS             | 1.08 (0.73)               | 0.79 (0.68)              | 0.0041* |
| Pulmonary VAS             | 1.08 (0.70)               | 0.56 (0.47)              | 0.0001**|
| Raynaud VAS               | 1.57 (0.86)               | 1.09 (0.81)              | 0.0001**|
| Digital ulcers VAS        | 1.70 (0.01)               | 1.05 (0.11)              | 0.0051* |
| Overall disease severity  | 1.57 (0.06)               | 1.25 (0.52)              | 0.0021* |

**VAS** – visual analogue scale. The significance value is based on the p-value < 0.05. * sign indicates the p-value < 0.05. ** sign indicates the p-value < 0.01.

Discussion

The HIIT in aerobic exercise affects biological responses such as the control and protection systems of the body. In addition, HIIT can also affect metabolic processes by increasing anabolic processes and helping in the metabolism of high-speed energy-supplying substrates in balance with energy expenditure and replenishment. This can help individuals in conditions of working ability, especially in more precise execution and speed of activities or work [17].

Respiratory muscle strength is a significant contributor to functional ability. An estimated 40% of patients with SSc have a forced vital capacity (FVC) less than 75%, showing the possibility of having a restrictive type of pulmonary disease. The decline in FVC occurs most rapidly in the first three to five years after the onset of the disease is diagnosed. Respiratory muscle function has contributed to the onset of dyspnea, limitation of exercise, deconditioning, and reduced quality of life [18].

Studies examining HIIT in aerobic exercise in the respiratory muscles also report significant increases in respiratory rate, as well as muscle strength and resistance, dyspnea, exercise capacity, and HRQoL. Moreover, training tests on ILD and pulmonary hypertension also showed an increase in exercise capacity, and decreased symptoms and quality of life after the addition of a respiratory muscle rehabilitation exercise program. In our study, significant results were obtained in the inspiratory strength of the muscles on examination with the SNIP method [12, 13, 19].

Systemic sclerosis severely affects physical, psychological, and social functions with quality of life. It was reported from a previous study, by de Oliveira et al. [20], that the greatest decrease in SF-36 in SSc patients appeared on the subscales for physical function and general health, while the psychological side was relatively high. Researchers suspect in this study that this unexpectedly high outcome in mental summary scores is due to poor psychological adaptation to chronic illness, thus masking the underlying condition and affecting other functions.

Up to 50% of patients with SSc complain of dyspnea. Potential causes of dyspnea in this population are gastroesophageal reflux and recurrent aspiration, ILD, airway disease, pulmonary hypertension, and other conditions such as anemia, obesity, arthritis, and/or decondition due to inactivity. Dyspnea and ILD were also reported as significant contributors affecting function and quality of life.

An earlier study by Khanna et al. [21] demonstrated a significant correlation between dyspnea and quality of life as assessed by the HAQ-DI and SF-36 questionnaires in SSc patients with ILD compared with healthy populations. Previous studies also reported that pulmonary involvement and dyspnea in scleroderma disease correlated with quality of life and functional status. It is reported that HAQ-DI and/or SF-36 should be included among the measurement results in scleroderma disease intervention [18].
However, in contrast to the study of Khanna et al. [22], a study by Chow et al. [22] demonstrated no significant correlation between functional status and pulmonary involvement parameters.

The Scleroderma-Specific Health Assessment Questionnaire Disability Index consists of HAQ-DI and is added with a 5-part VAS which consists of pulmonary disorders, digestive disorders, digital ulcers, Raynaud’s phenomenon, and overall disease severity. Steen et al. [23] used the HAQ DI on scleroderma patients and they found that the HAQ DI was unable to assess the multisystem effects of scleroderma, so they created the SHAQ with an added 5-part scleroderma-specific VAS.

Our study revealed significant changes in SSc patients after high-intensity aerobic exercise in all the SHAQ-DI VAS variables, except Disability Index. There is decreased blood flow in SSc patients due to muscle contraction of blood vessels so that the tissue in the fingers is ischemic and looks pale, red, or bluish, which is called Raynaud’s phenomenon. Ischemia that occurs due to decreased blood flow also causes the appearance of lesions on the fingers of SSc patients (digital ulcers).

The HIIT in aerobic exercise can improve vascular function and blood microcirculation [24] and also help the recurrence rate or severity of Raynaud’s phenomenon and digital ulcers experienced by SSc patients is significantly reduced as the results in this study were assessed using the SHAQ-DI VAS.

Physical activity increases digestive blood flow and increases intestinal contractions and increases the production of digestive enzymes. By decreasing the number of Raynaud’s attacks, digital ulcers, digestive and pulmonary VAS, it will affect the overall condition of the patient’s activity.

Murphy et al. [25] reported that the severity of gastrointestinal and joint involvement, level of pain, dyspnea, ineffective coping skills, low vital lung capacity, depressive symptoms, poorer physical and social function, and quality of sleep are correlated with fatigue levels, compressive symptoms, poorer physical and social function, and blood microcirculation [24] and also help the recurrence rate or severity of Raynaud’s phenomenon and digital ulcers experienced by SSc patients is significantly reduced as the results in this study were assessed using the SHAQ-DI VAS.

Conclusions

In our study on the intervention program of HIIT in aerobic exercise twice a week for 12 weeks it was considered to be safe for this population and proved to increase functional ability, respiratory muscle strength (SNIP), handgrip strength, walking speed (6MWT) increased MET values, and improved quality of life.

Since our study has a small sample size, we have to consider internal and external factors that influenced the results. Further study with a larger sample size and more exploration of the feasibility of combined exercise in SSc patients is recommended.

Acknowledgements

This study was supported by the Internal Grant Padjadjaran University (Grant Number: 3854/UN6.C/T/2019), and the authors would like to express their gratitude to Nurvita Sari for helping in the analysis and preparation of this study.

The authors declare no conflicts of interest.

References

1. Varga J. Systemic sclerosis (scleroderma). In: Goldman-Cecil Medicine. Goldman L, Schafer A (eds.). Elsevier, Philadelphia 2016: 1777–1785.
2. Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. Am Fam Physician 2008; 78: 961–968.
3. Avouac J, Fransen J, Walker UA, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis 2011; 7: 476–481, DOI: 10.1136/ard.2010.136929.
4. Vincent V, Dewi S, Gunadi WR. Correlation between serum procollagen type I N-terminal propeptide level with Modified Rodnan Skin Score in systemic sclerosis patients. Indones J Rheumatol 2017; 9: 1–5, DOI: 10.37275/ijrv912.70.
High-intensity interval training in systemic sclerosis subjects

5. Tani S, Juuti K, Kairavuori S. Integrating geography with physics and visual arts: analysis of student essays. Norsk Geografisk Tidsskrift 2013; 67: 172–178, DOI: 10.1080/00291951.2013.803258.

6. Nguyen C, Bézénaé A, Baubet T, et al. Association of gender with clinical expression, quality of life, disability, and depression and anxiety in patients with systemic sclerosis. PLoS One 2011; 6: e17551, DOI: 10.1371/journal.pone.0017551.

7. Ibn Yacoub Y, Amine B, Bensabbah R, Hajjaj-Hassouni N. Assessment of fatigue and its relationships with disease-related parameters in patients with systemic sclerosis. Clin Rheumatol 2012; 31: 655–660. DOI: 10.1007/s10067-011-1906-2.

8. de Oliveira NC, Portes LA, Pettersson H, et al. Aerobic and resistance exercise in systemic sclerosis: state of the art. Musculoskeletal Care 2017; 15: 316–323. DOI: 10.1016/j.msc.1185.

9. Mitropoulos A, Gumber A, Crank H, et al. The effects of upper and lower limb exercise on the microvascular reactivity in limited cutaneous systemic sclerosis patients. Arthritis Res Ther 2018; 20: 112, DOI: 10.1186/s13075-018-1605-0.

10. Defi IR, Jennie J, Vitriana V, Arisanti F. Translation and validation of Indonesia version of Scleroderma Health Assessment Questionnaire. Majalah Kedokteran Bandung 2020; 52: 45–52, DOI: 10.15395/mkb.v52n1.2004.

11. Johnson SR. New ACR EULAR guidelines for systemic sclerosis classification. Curr Rheumatol Rep 2015; 17: 32, DOI: 10.1007/s11926-015-0506-3.

12. Prigent H, Lejaille M, Falaize L, et al. Assessing inspiratory muscle strength by sniff nasal inspiratory pressure. Neurocrit Care 2004; 1: 475–478, DOI: 10.1385/NCC:1-4:475.

13. Kaminska M, Noel F, Petrof BJ. Optimal method for assessment of respiratory muscle strength in neuromuscular disorders using sniff nasal inspiratory pressure (SNIP). PLoS One 2017; 12: e0177723, DOI: 10.1371/journal.pone.0177723.

14. Fess EE. Grip strength. In: Clinical assessment recommendations, JS Casanova (ed.). American Society of Hand Therapists, Chicago 1992; 41–45.

15. Vandecasteele E, De Pauw M, De Keyser F, et al. Six-minute walk test in systemic sclerosis: a systematic review and meta-analysis. Int J Cardiol 2016; 212: 265–273, DOI: 10.1016/j.ijcard.2016.03.084.

16. Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler’s Index), Cambridge Pulmonary Hypertension Outcome Review (CAMP HOR), and Raynaud’s Condition Score (RCS). Arthritis Care Res (Hoboken) 2011; 63 (Suppl 11): S98–111, DOI: 10.1002/acr.20598.

17. Nuñez TP, Amorim FT, Beltz NM, et al. Metabolic effects of two high-intensity circuit training protocols: does sequence matter? J Exerc Sci Fit 2020; 18: 14–20, DOI: 10.1016/j.jesf.2019.08.001.

18. Caron M, Hoa S, Hudson M, et al. Pulmonary function tests as outcomes for systemic sclerosis interstitial lung disease. Eur Respir Rev 2018; 27: 170102, DOI: 10.1183/16000617.0102-2017.

19. Andrade FM, Oliveira AD, Lopes AI. Ventilation distribution as a contributor to the functional exercise capacity in patients with systemic sclerosis-associated interstitial lung disease without pulmonary hypertension. Braz J Med Biol Res 2019; 52: e8513, DOI: 10.1590/1414-431X20198513.

20. de Oliveira NC, dos Santos Sabbag LM, Ueno LM, et al. Reduced exercise capacity in systemic sclerosis patients without pulmonary involvement. Scand J Rheumatol 2007; 36: 458–461, DOI: 10.1080/03009740701605889.

21. Khanna D, Clements PJ, Purst DE, et al. Correlation of the degree of dyspnea with health-related quality of life, functional abilities, and diffusing capacity for carbon monoxide in patients with systemic sclerosis and active alveolitis: results from the Scleroderma Lung Study. Arthritis Rheum 2005; 52: 592–600, DOI: 10.1002/art.20787.

22. Chow S, Pope JE, Mehta S. Lack of correlation of the health assessment questionnaire disability index in systemic sclerosis associated pulmonary arterial hypertension. Clin Exp Rheumatol 2008; 26: 1012–1017.

23. Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997; 40: 1984–1991, DOI: 10.1002/art.1708041110.

24. Green DJ, Hopman MT, Padilla J, et al. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. Physiol Rev 2017; 97: 495–528, DOI: 10.1152/physrev.00014.2016.

25. Murphy SL, Kral TJ, Whiby I, et al. Fatigue and its association with social participation, functioning and quality of life in systemic sclerosis. Arthritis Care Res 1991; 4: 27–31, DOI: 10.1002/art.1790040106.

26. Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis Care Res 2001; 4: 415–422, DOI: 10.1002/acr.24122.

27. Paquette DL, Falanga V. Cutaneous concerns of scleroderma patients. J Dermatol 2003; 30: 438–443, DOI: 10.1111/j.1346-8138.2003.tb00413.x.