# Aerobic Exercise is Safe and Effective in Systemic Sclerosis

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- oxygen consumption
- oxygen saturation
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- quality of life

## Abstract

Several studies have established that systemic sclerosis patients have a reduced exercise capacity when compared to healthy individuals. It is relevant to evaluate whether aerobic exercise in systemic sclerosis patients is a safe and effective intervention to improve aerobic capacity. Seven patients without pulmonary impairment and seven healthy controls were enrolled in an 8-week program consisting of moderate intensity aerobic exercise. Patients and controls had a significant improvement in peak oxygen consumption (19.72 ± 3.51 vs. 22.27 ± 2.53 and 22.94 ± 4.70 vs. 24.55 ± 3.00, respectively, p = 0.006), but difference between groups was not statistically significant (p = 0.149). This finding was reinforced by the fact that at the end of the study both groups were able to perform a significantly higher exercise intensity when compared to baseline, as measured by peak blood lactate (1.43 ± 0.51 vs. 1.84 ± 0.33 and 1.11 ± 0.45 vs. 1.59 ± 0.25, respectively, p = 0.01). Patients improved the peak exercise oxygen saturation comparing to the baseline (84.14 ± 9.86 vs. 90.29 ± 5.09, p = 0.048). Rodnan score was similar before and after the intervention (15.84 ± 7.84 vs.12.71 ± 4.31, p = 0.0855). Digital ulcers and Raynaud's phenomenon remained stable. Our data support the notion that improving aerobic capacity is a feasible goal in systemic sclerosis management. The long term benefit of this intervention needs to be determined in large prospective studies.

## Introduction

Systemic Sclerosis (SSc) is a chronic rheumatic disease characterized by progressive fibrosis of the skin and circulation abnormalities (most notably Raynaud's phenomenon) involving multiple organ systems, including musculoskeletal, renal, pulmonary, cardiac, and gastrointestinal systems, with fibrotic and/or vascular complications [9].

It seems that sedentarism and some drugs used in the treatment of rheumatic disorders may have negative effects on the cardiovascular system, increasing the risk of cardiovascular disease in addition to other side effects, such as muscle weakening, which in turn may lead to deterioration of the physical condition [22]. Aerobic exercise has already been shown to be effective and safe for patients with cardiovascular and pulmonary chronic diseases [13]. Regarding rheumatic diseases, it has been well documented that exercise programs can improve aerobic capacity and muscle function in patients with rheumatoid arthritis, inflammatory myositis and fibromyalgia [4,10,16].

A recent review demonstrated that patients with mild to moderate systemic lupus and primary Sjögren syndrome who exercise at a moderate to high intensity level can benefit with regard to aerobic capacity, fatigue, physical function and depression [17].

Although several studies have established that SSc patients have a reduced exercise capacity when compared to predicted values of healthy individuals [2,;11,12,15,19,24], the effects of exercise on the cardiovascular system of SSc patients remains under investigation.

To our knowledge, this is the first prospective study of SSc patients concerning an exercise program. Therefore, the purpose of our study was to evaluate the effect of a supervised cardiovascular exercise in terms of exercise tolerance, aerobic capacity and quality of life in women with SSc.

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## Patients and methods

The medical histories of 250 outpatients from the Scleroderma Clinic of Rheumatology Division from the University of Sao Paulo School of Medicine were analyzed. To participate in this study, inclusion criteria were female gender, diagnosis of SSc according to the American Rheumatism Association criteria [18] and sedentarism for at least six months (defined by the lack of regular physical activity one or more times a week, as evaluated by the same researcher during individual interviews). Exclusion criteria were male gender, computed tomography (CT) evidence of pulmonary involvement, echocardiography evidence of cardiac impairment, pulmonary artery systolic pressure (PASP) equal to or above 40 mmHg, history of myositis, history of tobacco use, renal insufficiency, hypertension or anemia. Patients who presented symptoms like cough, dyspnea, thoracic pain, malabsorption, dysmotility and resting arrhythmia in a preliminary clinical examination were also excluded from our sample.

Pathologic lung impairment, also an exclusion criterion, was considered when forced vital capacity (FVC) (measured by spirometry) and diffusion lung capacity of carbon monoxide ($DL_{CO}$) (measured in a single-breath), were lower than 75 % of the predicted value.

Twenty-two patients qualified, of which nine agreed to participate and seven completed the study. They were 34–58 years of age, and all of them were currently taking D-penicillamine, pentoxifilline and diltiazem. None were taking corticosteroids or immunosuppressive drugs.

The SSc group had five patients with limited cutaneous SSc and two patients with the diffuse cutaneous form of the disease. Mean disease duration was 12.6 ± 7.1 years and mean modified Rodnan score [23] was 15.29 ± 7.85.

As a control group, we invited seven healthy women (as confirmed by medical history and clinical evaluation) who were employees of the Clinicas Hospital from the University of Sao Paulo School of Medicine. Control group volunteers were not taking any medication, were non-smokers and sedentary for at least six months.

All subjects gave written informed consent to participate in the study, which was approved by the Human Subject Protection Committee of Clinicas Hospital, University of Sao Paulo School of Medicine.

### Cardiopulmonary stress test

The exercise test was performed after a 2-h fast and 24-h caffeine abstinence. All subjects performed a cardiopulmonary stress test on a treadmill (Inbramed Millenium, RS, Brazil). Subjects underwent the test according to the conventional Bruce protocol [7], before and after the 8-week exercise program. This protocol has fixed increments in speed and incline at every three minutes, and was selected because it has been widely used for decades, including its use in populations with low physical fitness. Oxygen uptake ($VO_2$), production of carbon dioxide ($VCO_2$) and ventilation (VE) were determined by means of gas exchange on breath-by-breath basis in a computerized system (Aerosport-teem100, Ann Arbor, USA) with the Micromed ErgoPC Elite 3.2 (Brasília, Brazil) software. $VO_2$ peak was defined as the maximum attained $VO_2$ at the end of the exercise period in which the subject could no longer maintain the treadmill speed due to symptoms (dyspnea or fatigue) which precluded continuation of the test.

Anaerobic threshold (AT) was determined to occur at the break point between the increase of $VCO_2$ output and $VO_2$ (V-slope) or the point where the ventilatory equivalent for oxygen ($VE/VO_2$ ratio) was the lowest before a systematic increase. Respiratory compensation point (RCP) was determined to occur at the point which the ventilatory equivalent for carbon dioxide ($VE/VCO_2$ ratio) was the lowest before a systematic increase. Heart rate was monitored continuously by electrocardiogram. Arterial blood pressure was monitored non-invasively during rest and at peak exercise.

### Blood lactate concentration assessment

Blood lactate concentration was measured at all sessions at the earlobe site, and while at rest in all sample. We also registered the value of this variable in the final minute of the aerobic exercise, before the cool down period.

Measurements were taken with Accusport portable lactate analyzer (Boeringer Mannheim, Castle Hill, Australia).

### Oxygen saturation assessment

Oxygen saturation was measured at all sessions at the forefinger site, and while at rest in all sample. We also registered the value of this variable in the final minute of the aerobic exercise, before the cool down period.

Measures were taken with Moriya 1060 portable pulse oximeter (Moriya, Sao Paulo, Brazil).

### Quality of life assessment

To assess quality of life, we used the instrument WHOQOL-bref [21]. This instrument is available in 20 languages and has been validated in Portuguese by Fleck et al., 1999 [6].

### Exercise program

The exercise program lasted eight weeks. Subjects from the SSc and control groups underwent 40 min sessions, twice a week.

The intensity of the aerobic exercise was constantly monitored to ensure its performance within AT and 10 % before RCP from the cardiopulmonary test, according to a safety protocol developed for cardiac insufficient patients [14]. Heart rate was monitored with Polar monitors (A1 model, Kempele, Finland). The first five minutes of exercise were a warm-up period, where speed was progressively increased until target heart rate was reached. In the last five minutes of exercise a cool down was performed, decreasing speed until full stop.

In the first session, subjects performed 15 min of aerobic exercise within the target heart rate. In the second session, this time was increased to 20 min, 25 min in the third and 30 min in all subsequent sessions.

### Statistical analysis

Descriptive data are reported as means and standard deviations. In order to compare the groups' homogeneity concerning age and BMI, we used the Student's t-test for independent samples, single measures of asymmetry and shortness, and also the Shapiro Wilk test, which did not reject the hypothesis of a normal distribution of data. Since our sample was small, we also performed the non-parametric Mann-Whitney test, which also supported the validity of data and provided outcomes similar to other tests.

To evaluate the groups' evolution after the exercise program, a model of two-way analysis of variance (ANOVA) with repeated

**Table 1** Characteristics of systemic sclerosis and control groups.

| | SScG (n=7) | CG (n=7) |
|---|---|---|
| age (years)* | 45.57±8.22 | 43.29±4.89 |
| body mass index (kg/m²)** | 28.00±4.35 | 27.76±2.46 |
| race (% caucasian) | 85.71 | 85.71 |
| disease duration (years) | 12.57±7.06 | – |
| disease form (n, %) | | |
| diffuse | 2 (28.57) | – |
| limited | 5 (71.42) | – |

*p=0,539;**p=0,900. Values are mean±SD

**Table 2** Pulmonary and hemogram characteristics of systemic sclerosis group, classified by disease subtype.

| | Diffuse (n=2) | Limited (n=5) |
|---|---|---|
| pulmonary measures | | |
| FVC (% predicted) | 77.5±2.12 | 103.8±25.79 |
| $DL_{CO}$ (% predicted) | 79.5±2.12 | 96.4±13.86 |
| PSAP (mm Hg) | 35.5±0.70 | 33.2±3.27 |
| hemogram | | |
| Hb (mg/dl) | 12.45±0.07 | 13.34±1.03 |

FVC=forced vital capacity; $DL_{CO}$=diffusion lung capacity of carbon monoxide; PSAP=pulmonary artery systolic pressure; Hb=hemoglobin concentration. Values are mean±SD

measures taking two factors into consideration (group and time) was adjusted for each variable. The adopted significance level was 0.05.

The statistic software used for these calculations was SPSS for Windows, version 11.0.

## Results

There was no difference between groups with regard to age and BMI (**Table 1**). However, it is worth noting that there was a higher variability in the SSc group.

With regard to disease type, five of the seven subjects in the SSc group presented the limited form of the disease, while two had diffuse SSc. Mean disease duration time was 12.6 years (SD=7.1) with a minimum of three and maximum of 23 years of disease.

**Table 2** shows a descriptive analysis of the SSc group, showing that patients had a high mean of FVC and DLCO, a low PASP and no anemia.

There were no undesirable cardiovascular or locomotor side-effects in either the SSc or control groups throughout the program. Patients did not present increases in the incidence of digital ulcers or Raynaud's phenomenon during the exercise sessions. Rodnan score was similar before and after the intervention (15.84±7.84 vs. 12.71±4.31, p=0.0855). Both groups showed an adherence rate of 100%.

The general evaluation of quality of life revealed that there were no differences in this parameter regarding baseline and after the exercise program (p=0.150) for both groups.

At baseline, no significant differences were observed in either group regarding $VO_2$ peak and lactate parameters, whereas rest and peak oxygen saturation were lower in patients (p=0.032 and p=0.034, respectively).

The main physiological parameters of cardiopulmonary stress test are presented in **Table 3**. The SSc patients and controls demonstrated a significant improvement in their $VO_2$ peak (19.72±3.51 vs. 22.27±2.53 and 22.94±4.70 vs. 24.55±3.00, respectively; p=0.006 for time effect; and p=0.468 for interaction effect) after 8 weeks of exercise (**Fig. 1**), but there were no differences between the groups in both evaluations (p=0.149).

This finding is reinforced by the fact that at the end of the study the SSc and control groups were able to perform a significantly higher exercise intensity (1.43±0.51 vs. 1.84±0.33 and 1.11±0.45 vs. 1.59±0.25, respectively; p=0.01 for time effect; p=0.088 for group effect; and p=0.848 for interaction effect) when compared to the baseline, as measured by peak blood lactate (**Fig. 2**).

At the end of the study, resting oxygen saturation did not improve with exercise for either the SSc or the control group when compared to baseline data (90.71±5.79 vs. 92.43±8.42 and 97.00±1.15 vs. 97.43±0.53, respectively; p=0.481 for time effect; p=0.671 for interaction effect; and p=0.032 for group effect). On the other hand, peak exercise oxygen saturation showed higher values in the SSc group when compared to the baseline (84.14±9.86 vs. 90.29±5.09, p=0.048 for time effect; p=0.034 for interaction effect; and p=0.732 for group effect), as shown in **Fig. 3, 4**.

## Discussion

The purpose of this study was to investigate the effects of aerobic exercise in patients with SSc. Moderate intensity aerobic exercise significantly improved exercise capacity in our patients. Female SSc patients without pulmonary involvement have the potential to improve their aerobic capacity and to increase their effort oxygen saturation when assigned to a monitored aerobic exercise program. Thus, exercise may be considered a safe and powerful potential adjunct therapy for patients with SSc.

All patients in this study performed a maximal exercise test, achieving both ventilatory thresholds, at baseline and after the 8-week aerobic exercise program. None of our patients had arrhythmia either at rest or during the exercise test, as opposed to the findings of a previous study [2]. For our entire sample the reason for interrupting the test was cardiovascular fatigue, which supports the efficiency of this method for the improvement of $VO_2$ peak in patients and controls.

Adherence to the exercise program was 100% in both SSc and control groups. In the SSc group, the Rodnan score was similar before and after the intervention (15.84±7.84 vs.12.71±4.31, p=0.0855) and digital ulcers and Raynaud's phenomenon remained stable. This confirms that exercise seems to be safe for SSc patients, and it did not worsen the activity of the disease.

The lack of significant differences in the quality of life questionnaire at baseline and after the exercise program could be explained by the short duration of the exercise program or small sample size. The former may be more relevant, since in the present report, the exercise program lasted eight weeks whereas other studies with a longer period of exercise have shown evidence of increases in this parameter [3,20].

The increase in peak oxygen saturation is probably one of our most important findings. The most common functional impairment in patients with lung disease is impaired gas exchange [24]. In the early stages, oxygen saturation is normal at rest, but as exercise demands increases, oxygen desaturation may appear. After eight weeks of aerobic exercise, we observed a significant increase in the oxygen saturation of our patients, which did not occur in controls, as they already had a normal baseline value. Even without pulmonary impairment, our SSc patients pre-

**Table 3** Physiological parameters of cardiopulmonary stress tests of SSc and control groups.

| | Baseline | | After | |
|---|---|---|---|---|
| | SScG (n = 7) | CG (n = 7) | SScG (n = 7) | CG (n = 7) |
| HR peak (bpm) | 154.43 ± 20.97 | 171.14 ± 20.58 | 161.57 ± 15.22 | 169.43 ± 19.73 |
| $VO_2$ peak (ml/kg/min)* | 19.72 ± 3.51 | 22.94 ± 4.70 | 22.27 ± 2.53 | 24.55 ± 3.00 |
| % predicted $VO_2$ max | 58.33 ± 6.35 | 63.23 ± 9.11 | 62.04 ± 12.36 | 65.60 ± 6.47 |
| $VO_2$ AT (ml/kg/min)** | 12.49 ± 2.58 | 12.44 ± 2.29 | 10.51 ± 2.20 | 11.19 ± 2.17 |
| $VO_2$ RCP (ml/kg/min)*** | 14.84 ± 2.52 | 17.11 ± 4.62 | 16.26 ± 2.07 | 16.57 ± 4.59 |
| MET* | 5.63 ± 1.00 | 6.55 ± 1.34 | 6.36 ± 0.72 | 7.01 ± 0.85 |
| total test period (s) | 590.57 ± 137.77 | 659.43 ± 76.56 | 723.86 ± 74.36 | 713.57 ± 94.27 |

HRpeak = peak heart rate; $VO_2$peak = peak oxygen uptake; AT = anaerobic threshold; RCP = respiratory compensation point; MET = metabolic equivalent. Values are mean ± SD
One MET equals the resting metabolic rate of approximately 3.5 ml/kg/min
*p = 0.006 for time effect in both groups
**p = 0.012 for time effect in both groups
***p = 0.014 for SScG; p = 0.40 for CG (2-way ANOVA)

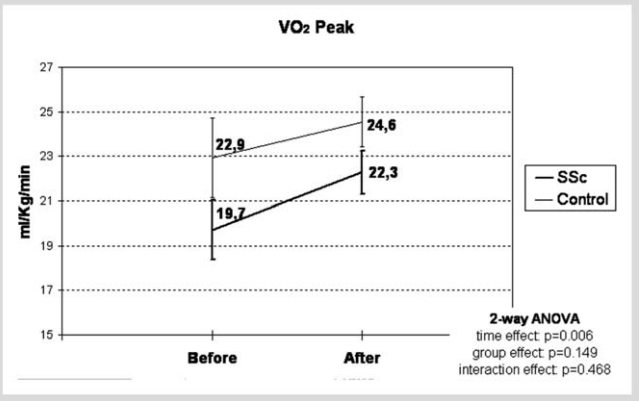


**Fig. 1** Peak oxygen consumption in SSc and control groups.

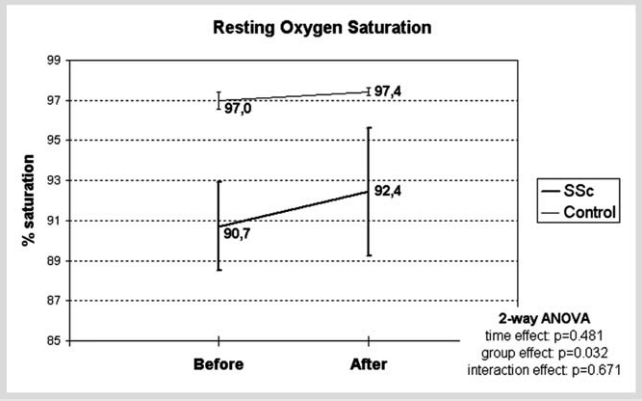


**Fig. 3** Resting oxygen saturation in SSc and control groups.

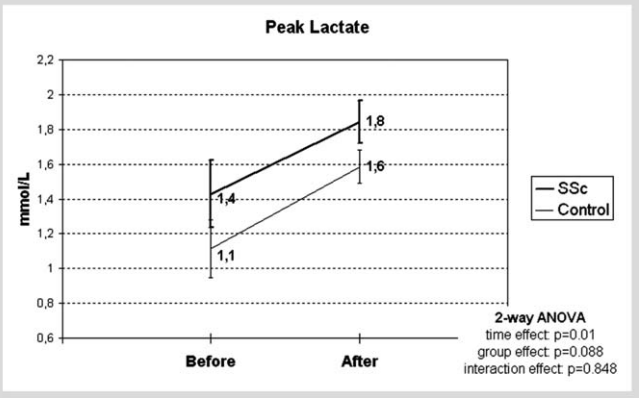


**Fig. 2** Peak lactate concentration in SSc and control groups.

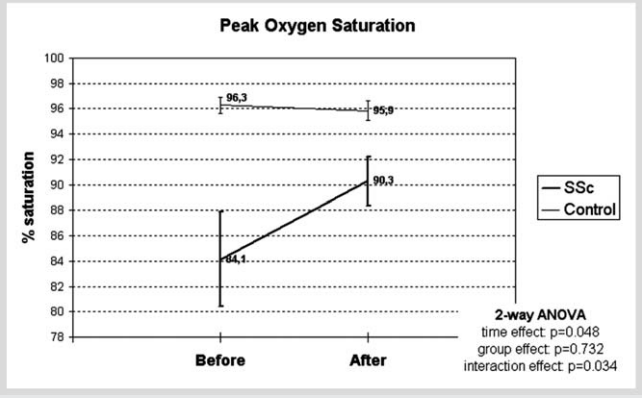


**Fig. 4** Peak oxygen saturation in SSc and control groups.

sented significantly lower resting oxygen saturation when compared to controls. After the program, patients had a significantly higher peak oxygen saturation, which increases the ability to perform daily tasks that demand aerobic capacity, such as walking.

Reduced oxygen transport can be caused by impaired ventilatory mechanisms or by metabolic changes [2]. As our SSc patients were sedentary, we speculate that the exercise program might have stimulated more efficient ventilatory mechanics, and this could explain the increased peak oxygen saturation.

This is also supported by the significant increase in peak blood lactate concentration after the exercise program. Physical exercise performed between AT and RCP makes muscles produce lactate, which needs to be removed for the subject to tolerate more exercise time [8]. At the end of the exercise program, SSc patients were able to remove acidosis more efficiently, thus improving their aerobic capacity. This might be due to an enhancement in ventilation, which led to a better gas exchange, and also to an improved muscle metabolism.

As the patients had no evidence of pulmonary involvement, no pulmonary hypertension and no anemia, the reduced peak oxygen saturation at baseline could be explained by some degree of pulmonary impairment, although it was not apparent in computed tomography, FVC and DLco. Two previous studies have raised the hypothesis that the lack of pulmonary involvement associated with some degree of exercise intolerance could be a

predictor of a future or occult pulmonary disease [1,12], which is very common in SSc.

The present study has some limitations. First, as SSc is a rare disease and also because our inclusion and exclusion criteria were very strict, especially regarding pulmonary involvement, our sample size was small. Secondly, although pulmonary involvement is very common in SSc [5], our patients did not present symptoms or signs of this condition, which might not reflect the usual clinical aspects of most SSc patients.

In conclusion, supervised cardiovascular exercise is well tolerated and significantly improves exercise tolerance, aerobic capacity, and oxygen saturation. Our data support the notion that achieving improved exercise capacity is a feasible goal in SSc management. The long term benefit of this intervention needs to be determined in large prospective studies.

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