# Cardiopulmonary Limitation to Exercise in Systemic Sclerosis: a Case-Control Study

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## Background

- Interstitial lung disease and pulmonary hypertension (PH) are the leading causes of morbidity and mortality in patients with systemic sclerosis (SSc).
- Cardiopulmonary exercise testing (CPET) offers a comprehensive approach to identify the cause of exercise limitation in patients with PH, chronic heart failure, or respiratory disease.
- CPET is proposed for early detection of pulmonary vascular disease in SSc patients but its role has not been extensively investigated.

## Purpose

To evaluate cardiopulmonary adaptation to exercise in SSc patients free from cardiac or pulmonary disease, in comparison with healthy subjects.

## Methods

- SSc patients with normal echocardiography and pulmonary functional test at rest, and healthy volunteers were prospectively enrolled between 07/2015 and 05/2018.
- They underwent maximal symptom-limited CPET.
- Results were compared after correction for age and gender.
- Data are expressed as mean ± SD or median (IQR) as appropriate.
- * indicates that non-parametric test was applied.

## Results

- Main characteristics of the study population are shown in Table 1.
- At peak exercise, patients had lower work rate and lower $VO_2$ than controls.
- Ventilatory efficiency (VE to VCO2 slope) was altered in patients compared with controls (Table 1, Figure 1).
- Asymptomatic patients displayed intermediate exercise abnormalities compared with those who reported some dyspnea at heavy exercise (Figure 2).

**Table1. Characteristics of study population**

| | SSc patients | Controls | p |
|---|---|---|---|
| N | 39 | 43 | |
| Female, N (%) | 36 (92%) | 31 (72%) | 0.023 |
| Age, years | 54 ± 12 | 46 ± 11 | 0.002 |
| BMI, $Kg.m^{-2}$ | 24 ± 4 | 24 ± 4 | 0.910 |
| Hypertension, N (%) | 8 (21%) | 3 (7%) | 0.106 |
| Smokers, N (%) | 6 (15%) | 5 (12%) | 0.749 |
| Lc-SSc<br>Dc-SSc<br>SSc sine scleroderma | 30 (77%)<br>7 (18%)<br>2 (5%) | | |
| Time from diagnosis, years | 6 (10) | | |
| Calcium channel blockers, N (%) | 15 (38%) | | |
| Giant capillaries, N (%) | 25 /32 (78%) | | |
| Positive anticentromeric antibodies, N (%) | 21/38 (55%) | | |
| NT-proBNP, pg/ml | 94 (88) | | |
| DLCO, % predicted | 68 ± 17 | | |
| DLCO/AV, % predicted | 77 ± 18 | | |

**Table2. Cardiopulmonary exercise testing**

| | SSc patients | Controls | p |
|---|---|---|---|
| Peak Workload, W | 70 (40) | 165 (85) | <0.001* |
| Peak Workload, % pred | 66 ± 24 | 108 ± 24 | <0.001 |
| Peak HR, % MHR | 90 ± 13 | 100 ± 8 | <0.001 |
| Peak RER | 1.27 ± 0.11 | 1.28 ± 0.10 | 0.570 |
| Peak VO2, ml/Kg/min | 16 (7) | 30 (14) | <0.001* |
| Peak VO2, % pred | 70 ± 19 | 106 ± 23 | <0.001 |
| VT1, ml/Kg/min | 11 (4) | 20 (9) | <0.001* |
| VT1, % peak VO2 | 71 ± 9 | 69 ± 12 | 0.558 |
| Peak VO2/HR, ml/bpm | 7(1) | 10 (7) | <0.001* |
| Peak VO2/HR, % pred | 75 ± 15 | 103 ± 22 | <0.001 |
| VE/VCO2 at VT1 | 40 ± 7 | 30 ± 3 | <0.001 |
| Pet CO2 at VT1, mmHg | 35 ± 5 | 41 ± 3 | <0.001 |
| VE/VCO2 slope | 41 ± 8 | 33 ± 5 | <0.001 |
| Peak VE, % MVV | 58 ± 15 | 72 ± 13 | <0.001 |
| Peak SpO2, % | 97 ± 3 | 96 ± 4 | 0.603 |

**Figure 2.** Comparison between subgroups of patients and control group for peak VO2 **(A)** and VE/VCO2 slope **(B).**

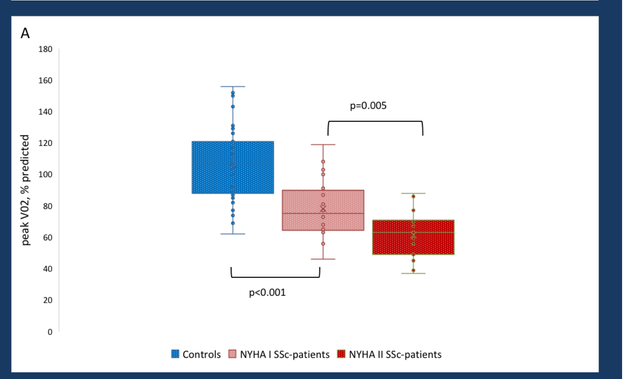
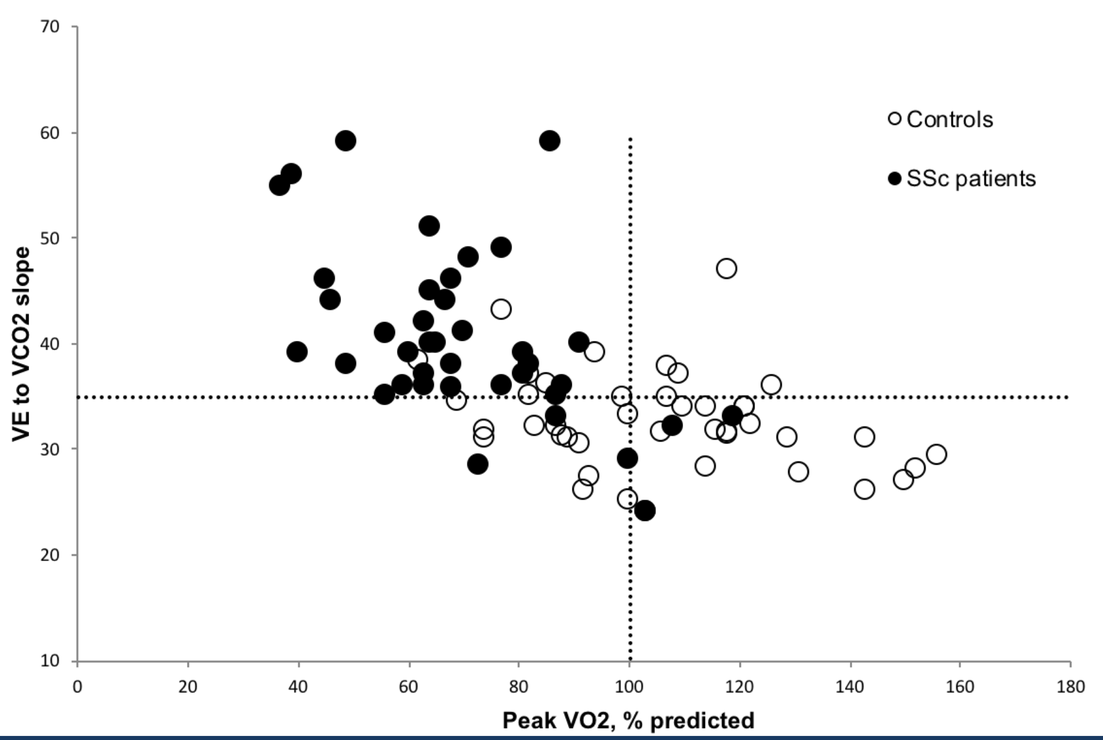



**Figure1. Relation between peak VO2 and VE/VCO2 slope in SSc patients vs controls**




## Discussion

- Our SSc patients showed exercise limitation in the absence of overt cardiac or lung disease.
- No patient was limited by lung capacity, as indicated by preserved ventilatory reserve at peak exercise.
- Lower $O_2$ pulse ($VO_2$/HR) could be explained by lower cardiac output or altered peripheral $O_2$ extraction at exercise in SSc patients.
- The high VE/VCO2 slope, high VE/$VCO_2$ ratio and low PetCO2 at ventilatory threshold (VT1) are usually reported in patients with pulmonary vascular disease, heart failure or interstitial lung disease, and are explained by ventilation to perfusion mismatch due to vascular or parenchymal alteration.
- Our data show that such abnormalities may be present in asymptomatic SSc patients, and may help for early detection of cardiopulmonary involvement.

## Conclusion

Systemic sclerosis patients, without overt cardiac or respiratory disease, present with cardiovascular limitation to exercise that may be related to latent cardiac dysfunction or pulmonary vascular disease.

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