Exercise tolerance in systemic sclerosis patients without pulmonary impairment: correlation with clinical variables

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ABSTRACT

Objective. *In systemic sclerosis (SSc) patients pulmonary vasculopathy (PV) is present in the early stage of disease and impairs dilation of affected pulmonary blood vessels, impeding pulmonary blood flow during exercise. Abnormal gas exchange findings were early investigated by cardiopulmonary exercise test (CPET).*

Methods. *A total of 34 female and 6 male [median age 49 (20–63) years] SSc patients with normal chest imaging and pulmonary function tests were enrolled. Twenty healthy controls age and sex matched [16 female and 4 male; median age 51 (35–73) years] were also recruited. All subjects underwent a full clinical examination, including a nailfold videocapillaroscopy (NVC). An incremental symptom-limited CPET was performed with estimation of minute ventilation (VE), workload (WR), peak oxygen uptake (pVO_2), and ventilatory efficiency (VE/VCO_2 slope).*

Results. *A reduced exercise tolerance (pVO_2 <80% of predicted) was documented in 18 out of 40 subjects (45%). Six out of 18 patients with a reduced exercise tolerance showed indirect signs of ventilation perfusion mismatch (VE/VCO_2 slope >34). Patients with digital ulcers (DUs) history showed VE/VCO_2 slope values significantly higher [31.4 (18–39.6)] than in patients without DUs history [26.9 (22–29.4)] ($p<0.0001$). VE/VCO_2 slope values also significantly differed between the three capillaroscopic groups: early [26.3 (18–29.4)], active [28 (26.8–39.6)], and late [32.9 (22.4–39)] ($p<0.0001$). A positive correlation was found between the VE/VCO_2 slope and both Disease Activity Index ($p<0.0001$, $r=0.59$) and Disease Severity Scale ($p<0.0001$, $r=0.73$).*

Conclusion. *In SSc patients without evidence of pulmonary and cardiac involvement, CPET might be useful in disclosing an early PV.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by endothelial dysfunction and fibrosis of the skin and internal organs. Endothelial dysfunction, microvascular and macrovascular damage are the hallmarks of SSc (1, 2), although the major cause of death still remains pulmonary involvement in terms of pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) (3, 4).

Pulmonary vasculopathy (PV) impairs dilation of pulmonary blood vessels, this feature being particularly magnified during exercise. Accordingly, in this setting of patients, an abnormal gas exchange due to ventilation-perfusion mismatch phenomena has been previously demonstrated through cardiopulmonary exercise test (CPET). Indeed, several studies showed a significantly reduced exercise capacity in those SSc patients with a clinically evident pulmonary impairment (5-9). Furthermore, Dumitrescu *et al*. also highlighted that, besides a PV, also a left ventricular dysfunction might be a usual underlying mechanism for a reduced exercise capacity in in SSc patients (10). On the other hand, early structural changes of pulmonary blood vessels might be present even in asymptomatic SSc patients with normal chest imaging and pulmonary function tests. However, up to now, exercise capacity in SSc patients without any significant heart or lung involvement has not been systematically studied yet.

Therefore, the aim of this study was to assess exercise tolerance in SSc patients without significant pulmonary and heart involvement. In addition, we sought to investigate the correlation

between CPET and main clinical variables of the disease.

Subjects and methods

Study design and population

Forty [34 female and 6 male; median age 49 (20–63) years] consecutive, non-smoker patients with SSc were enrolled in this study. All patients met the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative criteria for the classification of SSc (11). Patients with PAH, left ventricular dysfunction, pulmonary fibrosis, ILD, pulmonary venous occlusive disease (PVOD), chronic obstructive pulmonary diseases (COPD) were excluded. Subjects with relevant systemic comorbidities, such as an history of uncontrolled systemic hypertension, hyperlipidaemia, cardiac failure or valve diseases, hepatic failure, diabetes, cerebrovascular diseases, peripheral vascular diseases, coagulopathy and pregnant or breastfeeding women were not eligible and were also excluded.

Median duration of Raynaud's phenomenon (RP) and disease were 8 (2–34) years and 6.5 (1–21) years, respectively. Nineteen patients had limited cutaneous SSc (lcSSc) while 21 had diffuse cutaneous SSc (dcSSc), as defined by Le Roy *et al*. (12). Table I shows SSc patients' epidemiological and clinical features.

At the time of enrolment, all SSc patients were undergoing treatment with calcium channel blockers (nifedipine 30 mg/day), 17 were receiving prostanoid therapy and 11 Bosentan for digital ulcers prevention. None of the patients was treated with immunosuppressive agents (*e.g*. cyclophosphamide or mycophenolate mofetil or prednisone dose >10 mg/day).

Twenty healthy age- and sex-matched controls [16 female and 4 male; median age 51 (35–73) years] were recruited.

The subjects' written consent was obtained according to the Declaration of Helsinki and the study was conducted in agreement with local ethics committee directives.

Study procedures

– Baseline pulmonary function tests

Spirometric parameters of flows and volumes [(FEV1, forced expiratory volume in the 1st second), FVC (Forced vital capacity), FEV1/FVC)] and single-breath carbon monoxide (CO) diffusing capacity (DLCO), corrected for haemoglobin concentration, were recorded with a Quark PFT 2 spirometer (Cosmed) and expressed according to the standards recommended by the American/European Respiratory Society (13-14). All spirometric parameters are expressed as percentage of predicted.

Table I. SSc patients' epidemiological and clinical features.

Sex (female/male)	34/6
Age, years (median and range)	49 (20-63)
Body Mass Index (g/m^2)	25.6 (20-31)
Disease duration, years (median and range)	6.5 (1-21)
Raynaud's phenomenon duration, years (median and range)	8 (2-34)
Modified Rodnan total skin score (median and range)	11 (2-26)
Disease Activity index (median and range)	2 (0.5-8)
Disease Severity Scale (median and range)	5 (1-12)
dcSSc/lcSSc	21/19
SSc-specific autoantibodies, n (%)	
Anti-topoisomerase I	23 (57.5)
Anticentromere	9 (22.5)
None	8 (20)
Patients with digital ulcers history, n (%)	22 (55)
Number of digital ulcers/patients (median and range)	1 (1-4)
Capillaroscopic pattern, n (%)	
Early	13 (32.5)
Active	11 (27.5)
Late	16 (40)

Cardiopulmonary exercise test (CPET)

A maximal symptom-limited CPET was performed on an electronically braked cycloergometer (Ergoline-800, Mortara, Bologna, Italy), the subject wearing a nose clip and breathing through a mass flow sensor (Quark PFT, Cosmed, Rome, Italy) connected to a saliva trap. A personalized ramp exercise protocol was performed, aiming at a test duration of 10±2 minutes (15). The exercise was preceded by few minutes of resting breath-by-breath gas exchange monitoring and by a 3-minute unloaded warm-up.

Predicted values for peak oxygen uptake (pVO_2) were calculated according to the standard formula. The lactate threshold (LT) was identified through a V-slope analysis of VO_2 and carbon dioxide production (VCO_2), as well as of minute ventilation (VE), and it was confirmed through specific behaviour of O_2 (VE/VO_2) and CO_2 (VE/VCO_2) ventilatory equivalents and pressure end-tidal of O_2 ($PetO_2$) and CO_2 (PetCO2). The end of the isocapnic buffering period was identified when VE/VCO_2 increased and end-tidal pressure of CO_2 decreased. The relation between VO_2 and workload (VO_2/WR) was calculated as the slope of the linear relationship between $VO_2$and watt from the beginning of loaded exercise to the end of the exercise test. The relation between VE and VCO_2(VE/VCO_2 slope) was calculated as the slope of the linear relationship between VE and VCO_2 from one minute after the beginning of loaded exercise to the end of the isocapnic buffering period (16, 17).

CPET was self-terminated by the subjects when they claimed that they had achieved maximal effort. However, we considered maximal effort as achieved if the respiratory exchange ratio (RER), calculated as the ratio between VCO_2 and VO_2, was above 1.05. A 12-lead ECG, arterial systemic blood pressure, and arterial O_2 saturation (integrated pulse-oxymeter) were also recorded at baseline and during effort (18). All CPET were executed and analysed by two physicians blinded to patients' clinical features.

Radiologic assessment

High resolution computed tomography (HRCT) of the chest was performed at baseline and classified according to score of ground-glass opacities and fibrosis (19). The baseline HRTC was performed to exclude ILD and PVOD.

Doppler echocardiography

Doppler echocardiography was performed by a senior cardiologist. According to the European Society of Cardiology recommendations, systolic pulmonary arterial pressure (sPAP) was based on the tricuspid regurgitation. Pulmonary arterial hypertension was defined

Table II. Baseline pulmonary function tests parameters in SSc patients. All spirometric parameters are expressed as percentage of predicted.

	Healthy controls	SSc	SSc with DU	SSc without DU	Early	Active	Late
FVC %	107 (90-130)	103 (65-141)	97 (64-141)	109 (77-124)	109 (77-124)	103 (70-124)	97 (64-141)
FEV1 %	100 (91-149)	98 (70-134)	93 (70-134)	105 (75-122)	101 (75-122)	101 (75-121)	95 (70-134)
FEV1/FVC %	104 (89-116)	101 (78-121)	101 (88-121)	102 (78-111)	105 (94-119)	101 (78-114)	101 (88-121)
DLCO %	92 (83-104)	77 (55-110)	77 (55-104)	77 (58-110)	75 (58-104)	80 (63-110)	72 (55-104)

Data are presented as median (minimu-maximum range). FEV1: forced expiratory volume; FVC: forced vital capacity; DLCO: single-breath CO-diffusing capacity.

as systolic pulmonary artery pressure >36 mmHg on cardiac echocardiography and confirmed at right cardiac catheterisation (RHC) by a mean pulmonary arterial pressure (mPAP) of ≥25 mm Hg with a pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg (20).

Nailfold videocapillaroscopy

Nailfold videocapillaroscopy (NVC) was performed with a videocapillaroscope (Pinnacle Studio Version 8) equipped with a 500 × optical probe. The nailfold of the second, third, fourth and fifth finger was examined in each patient. According to Cutolo *et al*. patterns identified within the *SSc pattern* include: early, active and late (21).

Clinical assessment

Modified Rodnan total skin score (mRTSS) was chosen as the most used method to asses skin induration in SSc. It is determined at a standardised location of 17 different sites of the body with a standardised pinching method and it is scored from 0 to 3 (22). Disease activity in SSc was measured using Disease Activity index (DAI) which consists of 10 weighted variables: total skin score >14, scleroderma, digital necrosis, arthritis, total lung capacity <80%, erythrocyte sedimentation rate (ESR) >30, hypocomplementemia and changes in cardiopulmonary, skin and vascular symptoms in the past month (23). Disease severity was measured by Disease Severity Scale (DSS). This scale assesses disease severity in 9 organs or systems, namely general health, peripheral vascular, skin, joint/tendon, muscle and gastrointestinal tract, lungs, heart and kidneys. Each organ/system is scored separately from 0 to 4 depending on whether there is no, mild, moderate, severe or end-stage involvement (24).

Statistical analysis

An extension of the Shapiro-Wilk test of normality was preliminarily performed. All data are expressed as mean ± SD or as median and minimum-maximum range. Statistical comparison was performed between controls and SSc patients. The latter were therefore subdivided into two subgroups according to the DUs history (presence or absence) and capillaroscopic patterns (early, active and late). Categorical variables were compared with χ^2 test whereas the other variables were mostly compared by non-parametric Kruskal-Wallis test. The Bonferroni test was used in the *post hoc* analysis. Spearman's rank correlation coefficient (r) was used for bivariate analysis.

A *p*-value <0.05 was considered as statistically significant. All tests were two-sided. All data were evaluated with the database SPSS–PC+ (SPSS–PC+ Inc., Chicago, IL, USA).

Results

The baseline pulmonary function tests parameters in healthy controls and SSc patients were reported in Table II. The SSc median value of FEV1 was 98% (70–134%) of predicted, while FVC was 103% of predicted (65–141%). Median FEV1/FVC was 101% (78–121%), with no patients showing values <70% suggestive of a respiratory obstructive pattern. Median DLCO was 101% (78–121%), being 12 of 40 patients (30%) with DLCO values <70%.

All subjects performed a maximal CPET as documented by a RER higher than 1.05. Table III shows all the recorded CPET data in healthy controls and SSc patients. As expected, most of the CPET data were significantly better in the healthy controls than in the SSc group. Particularly in the latter group a reduced exercise tolerance, defined as a pVO_2 lower than 80% of maximum predicted, was found in 18 out of 40 subjects (45%) (Fig. 1). In this subgroup of SSc patients, a total of 6 patients (33%) showed a lower ventilatory efficiency, as assessed by a VE/VCO_2 slope higher than 34, suggesting a reduced exercise capacity due to a ventilation perfusion mismatch (Fig. 1). Conversely, no respiratory limitations to exercise were detected, none of the SSc patients showing a peak respiratory rate higher than 50 breath/min or a peak VE higher than the 90% of the maximal predicted VE.

Table III. Cardiopulmonary Exercise Test parameters in healthy controls and SSc patients.

	Healthy controls	SSc	*p*-value
pVO_2 (% predicted)	94 (83-115)	84.5 (52-109)	<0.001
pVE (% predicted)	78 (70-120)	51.5 (23-112)	<0.001
pWR (watts)	125 (80-240)	82.5 (30-180)	<0.0001
VE/VCO_2 slope	28 (21-33.6)	29.2 (18-39.6)	>0.05
VO_2/WR slope, ml/watt	9.3 (6-12)	9.9 (4.9-12.9)	>0.05
VO2 at LT (% pVO_2 predicted)	60 (50-80)	50 (30-60)	>0.05
RER	1.20 (1,06-1,27)	1.20 (1.1-1.4)	>0.05
SpO_2 (%)	98 (96-99)	97 (95-99)	>0.05

pVO_2: peak oxygen uptake; pVE: peak ventilation; pWR: peak workload; $PetCO_2$: pressure end-tidal of carbon dioxide; VE/VCO_2 slope: relation between VE and VCO_2; VO_2/WR slope: relation between VO_2 and workload; LT: lactate threshold; RER: respiratory exchange ratio; SpO_2: peak O_2 arterial saturation.

Twenty-two patients (55%) had a history of digital ulcers (DUs) with a median number of 1 (1-4). All CPET parameters of SSc patients with or without DUs are reported in Table IV. Particularly, patients with DUs history showed VE/VCO_2 slope values significantly worse ($p<0.0001$) than those of patients without DUs history (Table IV, Fig. 2).
Thirteen patients showed an early capillaroscopic pattern, 11 an active capillaroscopic pattern and 16 a late pattern. All CPET parameters of the three capillaroscopic groups of SSc patients are reported in table 5. Particularly, median values of VE/VCO_2 slope significantly differed ($p<0.0001$) in the three capillaroscopic groups, being progressively worse from early to late capillaroscopic pattern (Table V, Fig. 2).
No significant differences in exercise tolerance degree and CPET variables were observed in patients treated or not with Iloprost and Bosentan.
Spearman correlation disclosed a positive correlation between the VE/VCO_2 slope and age ($p<0.01$, r=0.45) and DAI ($p<0.0001$, r=0.59) and DSS ($p<0.0001$, r=0.73) (Fig. 2). No other significant correlations were observed between assessed CPET indices and clinical variables of disease (subset of disease, mRTSS, disease and Raynaud's phenomenon duration, BMI). Moreover, among pulmonary function variables (FEV1, FVC, FEV1/FVC, DLCO), as expected, only DLCO was negatively correlated with VE/VCO_2 slope ($p<0.01$, r=-0.44).

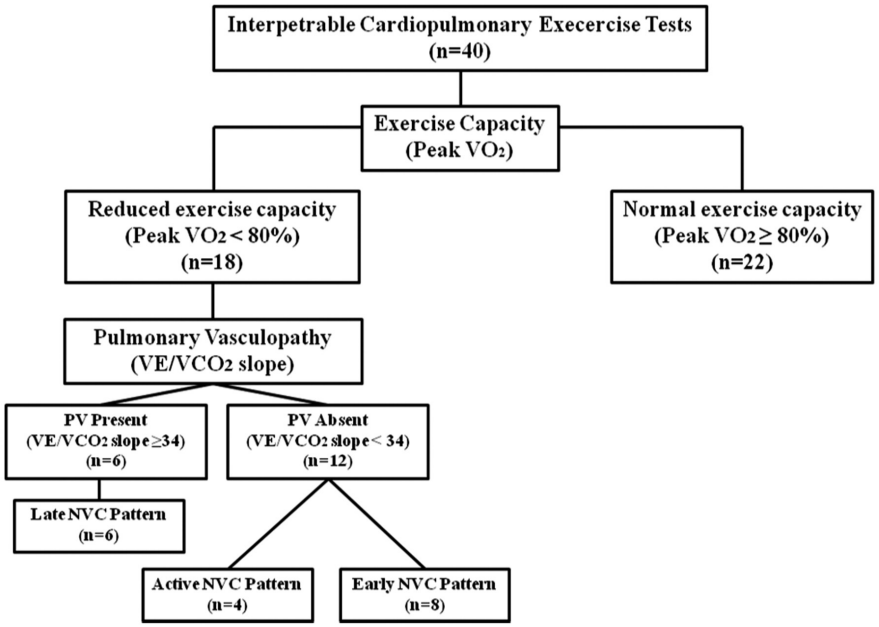

Fig. 1. SSc patients with normal and reduced exercise capacity.

Table IV. Cardiopulmonary Exercise Test parameters within the SSc group.

	SSc with DU	SSc without DU	*p*-value
pVO_2, (% predicted)	83 (52-100)	92 (54-109)	>0.05
pVE, (% predicted)	49.5 (28-71)	56.5 (23-112)	>0.05
pWR, (watts)	75 (30-145)	90 (50-180)	<0.01
VE/VCO_2 slope	31.4 (18-39.6)	26.9 (22-29.4)	<0.0001
VO2/WR slope, ml/watt	10 (6.6-12.9)	9.8 (4.9-12.7)	>0.05
VO2 at LT, (% pVO_2 predicted)	50 (30-60)	50 (30-60)	>0.05
RER	1.2 (1.1-1.4)	1.2 (1.1-1.3)	>0.05
SpO_2 (%)	97 (96-99)	96 (95-98)	>0.05

pVO_2: peak oxygen uptake; pVE: peak ventilation; pWR: peak workload; $PetCO_2$: pressure end-tidal of carbon dioxide; VE/VCO_2 slope: relation between VE and VCO_2; VO_2/WR slope: relation between VO_2 and workload; LT: lactate threshold; RER: respiratory exchange ratio; SpO_2: peak O_2 arterial saturation.

Table V. Cardiopulmonary Exercise Test parameters in three capillaroscopic patterns.

	Early	Active	Late	*p*-value
pVO_2 (% predicted)	79 (54-109)	91 (55-106)	83 (52-95)	>0.05
pVE (% predicted)	54 (23-94)	52 (28-112)	48 (28-71)	>0.05
pWR (watts)	90 (50-170)	90 (60-180)	70 (30-130)	<0.01
VE/VCO_2 slope	26.3 (18-29.4)	28 (26.8-39.6)	32.9 (22.4-39)	<0.0001
VO_2/WR, ml/watt	9.8 (7.4-12.7)	10 (4.9-11.7)	10 (6.6-12.9)	>0.05
VO_2 at LT (% pVO_2 predicted)	50 (30-60)	60 (30-60)	50 (40-60)	>0.05
RER	1.3 (1.0-1.4)	1.2 (1.1-1.4)	1.2 (1.1-1.3)	>0.05
SpO_2 (%)	97 (95-99)	97 (95-99)	97 (95-98)	>0.05

pVO_2: peak oxygen uptake; pVE: peak ventilation; pWR: peak workload; $PetCO_2$: pressure end-tidal of carbon dioxide; VE/VCO_2 slope: relation between VE and VCO_2; VO_2/WR slope: relation between VO_2 and workload; LT: lactate threshold; RER: respiratory exchange ratio; SpO_2: peak O_2 arterial saturation.

Discussion

Clinical observations and biologic studies support the hypothesis that PV plays a crucial role the SSc progression, from the very early onset of the disease through late clinical complications. Many of the internal organ SSc complications are vascular, including PAH and scleroderma renal crisis. Indeed, structural vascular damage occurs in many vascular districts and contributes to pulmonary, renal, cardiac and gastrointestinal complications (25).
The frequent occurrence of vascular and parenchimal lung impairment in SSc is likely to contribute to gas-exchange abnormalities, mainly leading to a reduced exercise capacity (10). Our present study showed, even in a cohort of SSc patients without cardiac and pulmonary involvement, a high prevalence of reduced exercise capacity (nearly 45% of the study sample), in terms of pVO_2 values <80% of the predicted. Interestingly, more than one third of these patients (15% of the total study sample) showed ventilation-perfusion mismatch

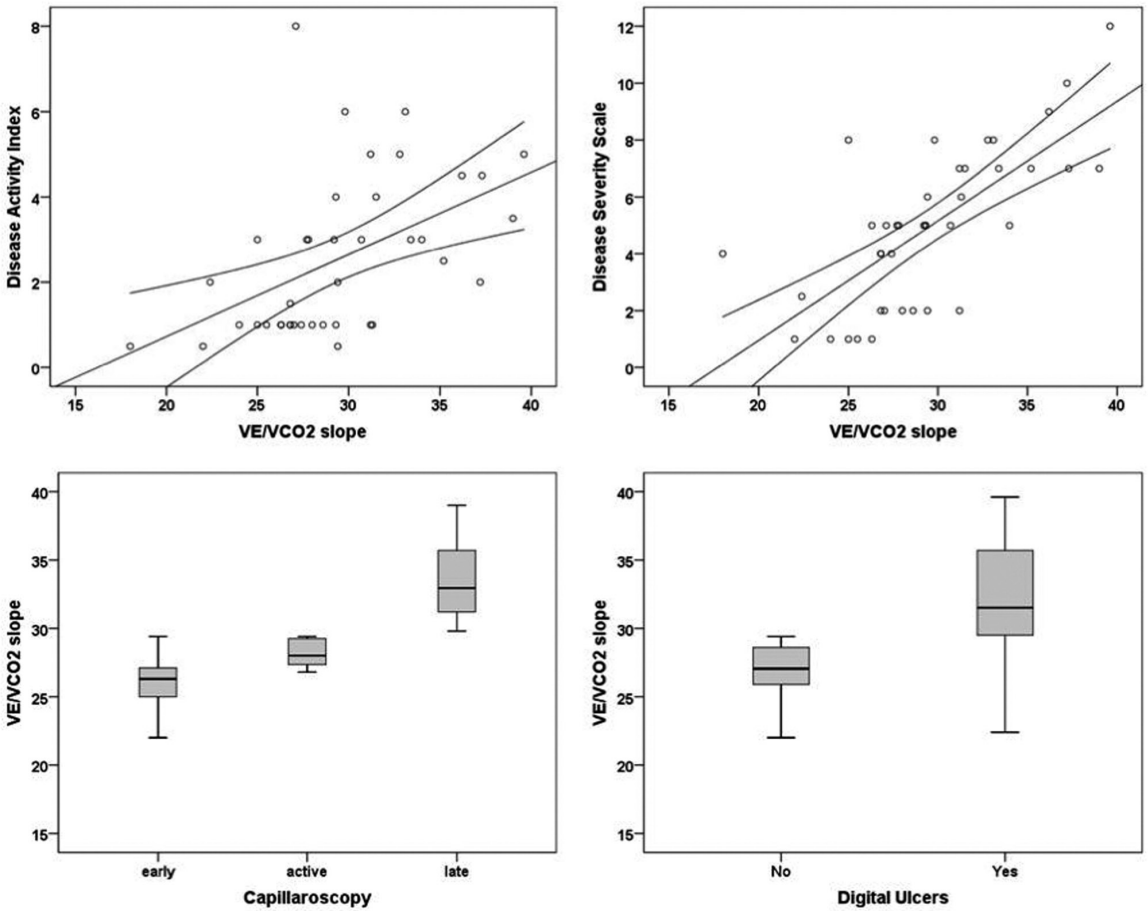

Fig. 2.
Correlation between VE/VCO_2 slope and clinical variables of SSc disease.

phenomena during exercise, as suggested by VE/VCO_2 slope values >34, indirectly suggesting the presence of an early pulmonary vasculopathy (PV). This datum might be of clinical interest given that at least a 15% of patients with SSc with normal resting pulmonary function were reported to suffer of gas exchange abnormalities during exercise, thus suggesting that CPET might be more sensitive to understand possible mechanisms underlying a functional limitations in these patients (26).

Traditionally, pVO_2 has been considered as the gold standard variable in CPET for prediction of cardiovascular events in several cardiovascular and not cardiovascular disease (27, 28). However, pVO_2 prognostic accuracy has been challenged in the last decade and the VE/VCO_2 slope has been shown to be strongly related to the alveolar-capillary membrane dysfunction and it has been proven as a powerful and independent predictors of outcome, particularly in patients with congestive heart failure (CHF) (29-31). Specifically, a VE/VCO_2 slope value equal to 34 has been demonstrated a useful cut-off to identify CHF patients at high risk of death or re-hospitalisation. However, more recent literature suggests that the risk increases continuously with VE/VCO_2 slope values (32).

In patients with an early PV, such as those we those studied, exercise capacity is usually markedly reduced with a typical CPET pattern characterised by a reduced pVO_2 with a high VE/VCO_2 slope (8). Indeed, SSc patients may develop exercise intolerance due to musculoskeletal involvement, restrictive lung disease, left ventricular dysfunction, or PV. Very few studies have been published about the exercise performance in SSc. Schwaiblmair *et al*. suggest that occult pulmonary impairment may be present in patients with normal pulmonary function and that cardiopulmonary exercise testing enables the detection of such impairment (26). Dumitrescu *et al*. demonstrated that previously undiagnosed exercise impairments due to left ventricular dysfunction or PV were common in SSc patients and CPET may help to early differentiate and detect these disorders (10). Moreover, Harðardottir *et al*. confirm that cardiocirculatory limitation is the main factor for exercise intolerance in SSc and that exercise intensifies systemic inflammation and oxidative stress in patients with SSc (33). The CPET associate with RHC may discriminate the etiology of dyspnea and exercise intolerance in selected SSc patients with non-diagnostic preliminary testing (34-36).

In our study we demonstrated that the VE/VCO_2 slope correlates with disease severity and activity, thus suggesting a relationship between this marker of ventilation-perfusion mismatch with SSc severity (37). We showed for the first time that, in a cohort of SSc patients without signs of cardiopulmonary involvement, the VE/VCO_2 slope correlates with digital vascular damage (capillaroscopic damage and the presence of DUs). Since many of the severe internal organ complications of SSc are vascular, we can assume that our data argue in favour of an initial manifesta-

tion of lung damage (38-41). Indeed, it might be hypothesised that patients with more severe vascular involvement could be non-invasively identified through a late NVC pattern and high VE/VCO_2 slope values. However this does not permit valid conclusions and only longitudinal studies allow validation of prognostic factors.

In conclusion, our data suggest that in SSc patients CPET, and particularly the VE/VCO_2 slope, might be useful in the early detection of PV presence. Larger studies are needed to confirm these results.

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