Phenotyping Exercise Limitation in Systemic Sclerosis: The Use of Cardiopulmonary Exercise Testing

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Key Words

Systemic sclerosis · Exercise capacity · Cardiopulmonary exercise testing · Left ventricular dysfunction · Pulmonary vasculopathy

Abstract

Background: Exercise impairment is a common symptom of systemic sclerosis (SSc), a disorder which is frequently complicated by cardiopulmonary involvement. **Objectives:** This study's aims were: (a) to define the prevalence and the potential causes of limited exercise capacity and (b) to study potential differences in clinical, radiological and functional characteristics and blood serology among SSc patients with exercise limitation of different etiology. **Methods:** Prospectively collected data on SSc patients who had conducted full lung function testing, blood serology, thorax high-resolution computed tomography, Doppler echocardiogram and a maximal cardiopulmonary exercise testing (CPET) were retrospectively analyzed. Using a CPET algorithm, patients were

characterized as having normal or subnormal exercise capacity (N), respiratory limitation (RL), left ventricular dysfunction (LVD) or pulmonary vasculopathy (PV). Group comparisons were conducted using either one-way ANOVA or the Kruskal-Wallis test. A p value <0.05 was considered significant. **Results:** The study population consisted of 78 patients (53.7 ± 13.7 years old; 10.3% male). PV was present in 32.1%, LVD in 25.6% and RL in 10.2%, while 32.1% of the patients constituted the N group. The presence of antisclero-70 antibodies, low anaerobic threshold and low peak exercise capacity measures could discriminate LVD from the other groups. Low end-tidal carbon dioxide pressure and its change from rest to anaerobic threshold could discriminate between the PV, LVD and N groups, while respiratory restriction along with ventilatory inefficiency indices could differentiate the RL group from the rest. **Conclusions:** The combined evaluation of CPET gas exchange patterns with baseline measurements could discriminate the causes of exercise limitation among SSc patients.

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Introduction

Systemic sclerosis (SSc) is a connective tissue multi-system disorder of unknown etiology, characterized by the presence of autoantibodies, vascular damage and organ fibrosis [1, 2]. Pulmonary involvement is frequent among patients with SSc, and it most usually manifests as interstitial lung disease and/or pulmonary vasculopathy (PV), leading to pulmonary arterial hypertension [3]. Cardiac abnormalities are also common in SSc, including conduction system defects, pericardial effusion and myocardial ischemia, hypertrophy or failure [4, 5]. In the past few decades and following the better management of scleroderma renal crisis, cardiopulmonary complications have become the major factor in the severity of the disease, representing the leading cause of death for SSc patients [6]. Preliminary symptoms of cardiopulmonary involvement such as exertional dyspnea and fatigue are subtle and nonspecific and overlap with those of other morbidities of SSc, including esophageal dysmotility, myositis or chest wall disorders. Given the multifactorial cause of exercise impairment and the high mortality rates of heart and chest disease, the identification of patients with early cardiopulmonary complications is challenging and may be important for the management and survival of SSc individuals.

Cardiopulmonary exercise testing (CPET) provides an objective and quantitative evaluation of a subject's functional capacity, allowing the evaluation of the individual impact of pulmonary and cardiac disorders on exercise performance [7]. Although previous studies have utilized CPET to investigate the maximal exercise capacity of patients with SSc [8–10], little data exist regarding the test's potential to differentiate between various causes [respiratory limitation (RL), PV or cardiac dysfunction] of exercise impairment. In a previous study where CPET and right heart catheterization were utilized, the potential causes of exercise limitation were identified; however, the study sample was relatively small [11]. Moreover, Dumitrescu et al. [12] studied whether signs of PV could be distinguished from other causes of exercise limitation during CPET, but only patients without obvious cardiac and pulmonary involvement were included in the study cohort.

Against this background of uncertainty, we conducted a retrospective study aiming at: (a) estimating the prevalence of decreased maximum exercise capacity during maximal CPET, (b) investigating the cause of this functional limitation, based on distinct gas exchange patterns and (c) studying potential differences of clinical, radio-

logical and functional characteristics and blood serology among scleroderma patients with exercise limitation of different etiology.

Material and Methods

Study Population

We performed a retrospective analysis of routinely collected patient data. The final study population consisted of clinically stable patients with SSc, diagnosed according to the American College of Rheumatology guidelines [13], who were referred to the Respiratory Failure Unit for functional evaluation, between March 2008 and March 2013, due to perceived exertional dyspnea or decreased physical performance. Patients were characterized as clinically stable, when they presented with stable symptoms and signs of SSc without any major complications or other acute events for which they had to change treatment modalities or be hospitalized, for at least 3 months before entering the study protocol. Patients with both types of SSc (diffuse SSc or limited SSc) were included in the study. Patients who, during the initial screening, were found to have absolute contraindications for CPET, such as unstable angina, uncontrolled arrhythmias causing symptoms, severe aortic stenosis, a room air saturation <85%, severe untreated arterial hypertension at rest (systolic blood pressure >200 mm Hg, diastolic blood pressure >120 mm Hg), hypertrophic cardiomyopathy, significant orthopedic impairment that compromises exercise performance and mental impairment [7], did not undertake CPET, while those with clinical signs of heart failure (such as pulmonary or peripheral edema), left ventricular ejection fraction <55% and/or severe valvular disease were excluded from further analysis. The institution's Bioethics Committee approved the retrospective analysis of these routinely collected patient data.

Study Measurements

Serology and Imaging

Chest high-resolution computed tomography (HRCT) and blood serology (the measurement of anticentromere antibodies (ACA) and anti-sclero70 antibodies) had been conducted in all patients for diagnostic purposes within 6 months prior to their referral. Pulmonary fibrosis was characterized as limited when it occupied <20% of the lung parenchyma and as extended when it occupied >20%, according to a previously published staging system [14].

Pulmonary Function Testing

All subjects underwent full pulmonary function testing (PFT) at the Respiratory Failure Unit. The MasterScreen PFT Jaeger spirometer was utilized to undertake lung function studies. Forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio, functional residual capacity (FRC), inspiratory capacity (IC), total lung capacity (TLC), carbon monoxide diffusing capacity (DLCO) and carbon monoxide transfer coefficient (KCO) were measured. The DLCO and KCO predicted values were further adjusted for hemoglobin concentration (DLCOc and KCOc, correspondingly), according to previously published equations [15]. The maximum voluntary ventilation (MVV) was indirectly estimated by the equation: $MVV = FEV_1 \times 40$ [7].

Fig. 1. Categorization of SSc patients into the N, RL, LVD and PV groups, using CPET parameters.

Echocardiography

The patients underwent a complete resting transthoracic echocardiography taken by an experienced investigator within 1 h prior to CPET. It included two-dimensional, pulsed and continuous-wave Doppler and color flow imaging using a real-time, phased array sector scanner (model Sonos 5000; Hewlett-Packard, Andover, Mass., USA). The echocardiographic study included the evaluation of the right and left ventricular and atrial dimensions, left ventricular ejection fraction and valvular function. Systolic pulmonary artery pressure (sPAP) was calculated from the maximum velocity of the tricuspid regurgitant jet using the Bernoulli equation and then adding to this value an estimated right atrial pressure based on the size of the inferior vena cava and the change in caliber of this vessel with respiration [16]. Pulmonary hypertension was defined by sPAP >35 mm Hg at rest [17].

Cardiopulmonary Exercise Testing

All patients performed an incremental CPET to maximum tolerance on a cyclic ergometer. Heart rate (HR), pulse oximetry and a 12-lead electrocardiogram were continuously recorded, while systolic and diastolic blood pressures were measured every 2 min, using a cuff sphygmomanometer. The exercise protocol included 3 min of rest, 3 min of unloaded pedaling at 50–60 rpm and a ramp

protocol with increasing work rate (WR) from 10 to 15 watts/min, until the subjects reached their symptom-limited maximum [18]. Gas exchange values and exercise parameters were collected breath-by-breath (Cardiopulmonary Metabolic Cart, Medical Graphics) and were computer-averaged over 10-second intervals. Oxygen uptake (VO₂), minute ventilation (V_E), tidal volume, respiratory rate and end-tidal carbon dioxide partial pressure (PETCO₂) were directly measured, while oxygen pulse (VO₂/HR) and ventilatory equivalent for carbon dioxide at anaerobic threshold (AT; VE/VCO₂@AT) and at peak VO₂ (VE/VCO₂@VO₂ peak) were calculated based on the same technique. The AT was derived from a VO₂-VCO₂ plot and was identified as the point where VCO₂ started to increase faster than VO₂, as previously described [12, 19, 20]. The AT's normal predicted values were determined utilizing previously published equations [21]; the AT % predicted values were calculated as the percentage of measured to normal predicted values. The breathing reserve (BR) was determined as MVV – V_E peak [7].

Categorization of Exercise Impairment

A CPET algorithm, a shorter version of what had been previously used to identify PV among SSc patients [12], was applied in order to categorize exercise impairment. Patients were separated

in four categories: (a) normal exercise capacity or subnormal but not limited by evident heart or lung disease (N), (b) RL, (c) left ventricular dysfunction (LVD) and (d) PV (fig. 1).

All patients with normal peak VO_2 ($\geq 80\%$ predicted) [7], normal AT ($\geq 75\%$ predicted), normal BR (≥ 11 liters), normal VE/VCO_2 at AT (< 34) and no resting hypoxemia [rest arterial oxygen saturation (SPO_2) $\geq 95\%$] nor exercise-induced hypoxemia ($\Delta\text{SPO}_2 = \text{rest SPO}_2 - \text{peak SPO}_2 \leq 4\%$) [7, 12, 21] were included in the group of normal exercise capacity (N group). Patients with normal AT, normal VE/VCO_2 at AT and no hypoxemia, but with low peak VO_2 ($< 80\%$ predicted), were also included in the same category, i.e. in the group of those who, even though they had subnormal exercise capacity, were not limited by evident heart or lung disease [12]. Patients with a low BR (< 11 liters) and peak $\text{V}_E/\text{MVV} > 85\%$ or peak tidal volume/IC $> 85\%$ were categorized in the RL group, irrespectively of peak VO_2 , AT, VE/VCO_2 and SPO_2 values [7]. Patients with decreased peak VO_2 ($< 80\%$ predicted) and decreased AT ($< 75\%$ predicted) were categorized in the LVD group, when they had normal VE/VCO_2 at AT (< 34) or high VE/VCO_2 at AT (≥ 34) with increasing or neutral ΔPETCO_2 (i.e. the change of PETCO_2 from rest to AT) [7, 12], without resting nor exercise-induced hypoxemia. The PV category included patients with reduced peak VO_2 , reduced AT, high VE/VCO_2 at AT and decreasing ΔPETCO_2 with or without hypoxemia. Patients with normal peak VO_2 and AT but with ventilation-perfusion mismatching (abnormal VE/VCO_2 at AT and decreasing ΔPETCO_2) [7] were also grouped as emerging PV.

Statistical Analysis

Standard equations were used to calculate the normal predicted values of lung function and CPET parameters [7, 22, 23]. All analyses were performed using the Predictive Analytics Software (PASW, SPSS Inc.) version 18. Data distribution was assessed using the Shapiro-Wilk test of normality. Variables are presented as mean percent predicted (% predicted) ± 1 SD, as mean ± 1 SD or as median (minimum–maximum). Group comparisons for continuous variables were conducted using one-way ANOVA or the Kruskal-Wallis test, according to their distribution; the Gabriel post-hoc test was used due to different group sizes compared and equal distribution of variances assumed for the parametric comparisons and the Tukey HSD for the nonparametric ones. Group comparisons for categorical variables were conducted utilizing the χ^2 test. A p value < 0.05 was considered significant.

Results

The initial study population consisted of 82 patients. One patient was unable to complete the maximum exercise due to discoordination with the bike, while another 3 patients only reached their ‘submaximal’ levels due to joint pain and stiffness, so they were excluded from the analysis. Thus, the final study population consisted of 78 patients (53.7 ± 13.7 years old; 10.3% male). The baseline demographics of the study population are presented in table 1. Thirty-eight patients (48.7%) presented with diffuse SSc, while the rest had limited SSc, according to their

Table 1. Baseline characteristics of the study population (n = 78)

Age, years	53.7 $\pm$ 13.7
Gender, n (%)	
Male	8 (10.3)
Female	70 (89.7)
BMI	27.7 $\pm$ 5
Thorax HRCT, n (%)	
Limited or no fibrosis	58 (74.4)
Extensive fibrosis	20 (25.6)
Type of SSc, n (%)	
Limited cutaneous	40 (51.1)
Diffuse cutaneous	38 (48.7)
Serum antibodies, n (%)	
ACA positive	19 (24.4)
Anti-sclero70 positive	40 (60.3)
FEV ₁ , % predicted	87.9 $\pm$ 19.5
FVC, % predicted	83.9 $\pm$ 18.4
FEV ₁ /FVC	86 $\pm$ 7.2
IC, % predicted	80.5 $\pm$ 26.7
FRC, % predicted	81.8 $\pm$ 23.1
TLC, % predicted	74.9 $\pm$ 16
DLCOc, % predicted	60.6 $\pm$ 18.6
KCOc, % predicted	81.9 $\pm$ 18.3
sPAP, mm Hg	32 (20–70)
Rest SPO ₂ , %	97.9 $\pm$ 1.6

medical history, which had been provided by their consultant rheumatologist. The cause of exercise impairment was determined following the algorithm presented in figure 1. The majority of SSc patients (32.1%) presented with PV, 25.6% presented with LVD, while the least frequent cause of exercise impairment was RL (10.2%). Twenty-five patients (32.1%) had either normal exercise capacity or were not limited by evident heart or lung disease (N group).

Baseline Characteristics according to Exercise Impairment Categorization

Table 2 presents age, gender, body mass index (BMI), PFTs, serology and imaging data by diagnostic categories. Serum antibodies were of some interest for group discrimination; the vast majority of LVD patients were negative to ACA and positive to anti-sclero70 antibodies, and this difference reached statistical significance between the LVD and RL groups.

Several differences were recorded regarding PFTs. FEV₁ % predicted, FVC % predicted and TLC % predicted were significantly lower among the RL group compared to the rest of the groups, while IC % predicted and FRC % predicted discriminated the RL from either the PV

Table 2. Demographics, PFTs, serology and imaging data, grouped by exercise limitation category

	N (n = 25)	LVD (n = 20)	PV (n = 25)	RL (n = 8)	p
Age, years	51±13.5	50.6±15.6	55.5±13.2	62.6±8.6	0.130
Gender, %					
Male	12	5	12	12.5	0.847
Female	88	95	88	87.5	
BMI	29.1±4.2	26.7±5.4	27.6±4.6	28.2±4.2	0.257
FEV ₁ , % predicted	96.8±17.7 [#]	82.7±17 ^{#*}	91.3±17.8 [#]	60.9±14.6 [*]	<0.001
FEV ₁ /FVC	84.5±8	86.9±7.4	87.6±6.7	83.9±6.6	0.430
FVC, % predicted	94±14.4 [#]	78.8±15.7 ^{*,*}	85.6±17.7 [#]	57.2±13.3 [*]	<0.001
IC, % predicted	91.6±23.8 [#]	78.4±19.8	82±24.9 [#]	52.8±28 [*]	<0.002
FRC, % predicted	89.3±16.4 [#]	75.8±30.4	87±19.4 [#]	60.3±23.5 [*]	<0.014
TLC, % predicted	84.6±13.3 [#]	70±16 [#]	76.7±13.9 ^{*,#}	54.6±11.7 [*]	<0.001
DLCOc, % predicted	71.8±15.1	52.9±17 [*]	62.3±18.3	45.8±22.4 [*]	<0.001
KCOc, % predicted	85.7±21.5	80.7±12.1	83.3±16	81.2±27.7	0.532
sPAP, mm Hg	25 (20–42)	35 (20–51) [*]	35 (21–55) [*]	40 (32–57) [*]	<0.001
ACA antibodies, %					
Positive	28	15	32	75	0.815
Negative	72	85	68	25	
Anti-sclero70 antibodies, %					
Positive	44	85	60	25 [^]	<0.048
Negative	56	15	40	75 [^]	
Thorax HRCT, %					
Limited fibrosis	85 [#]	60	92	25	
Extensive fibrosis	15 [#]	40	8	75	<0.049

p: for overall comparisons between the four groups. * p < 0.05 for comparisons between the N group and the other groups. ^ p < 0.05 for comparisons between the LVD group and the other groups. # p < 0.05 for comparisons between the RL group and the other groups.

Table 3. Parametric comparisons of exercise parameters grouped by category of exercise limitation

	N (n = 25)	LVD (n = 20)	PV (n = 25)	RL (n = 8)	p
Peak WR, % predicted	80.6±18.7 [^]	49±24.5 [*]	71.6±24.4 [^]	53.5±24.2 [*]	<0.001
Peak VO ₂ , ml/kg/min	16.8±4.1	13.2±3.8 [*]	15.7±2.5	12.5±3.4 [*]	0.002
AT, ml/kg/min	12.3±2.1 [^]	9±2	11.5±2 [^]	10.2±2.8	<0.001
AT, % predicted	92.9±10.8 [^]	63.9±8.4 [*]	82.5±16.5 [^]	78±26.4 [*]	<0.001
PETCO ₂ @rest	35.3±2.7	33.6±3.5	33.2±1.9	32.3±1.8	NS
ΔPETCO ₂	3.7±3.1 ^{#,~}	2.1±1.94 ^{#,~}	-0.6±0.6 [*]	-2.5±3.3 [*]	<0.001

p: for overall comparisons between the four groups. * p < 0.05 for comparisons between the N group and the other groups. ^ p < 0.05 for comparisons between the LVD group and the other groups. ~ p < 0.05 for comparisons between the PV group and the other groups. # p < 0.05 for comparisons between the RL group and the other groups.

Table 4. Nonparametric comparisons of CPET parameters between SSc patients grouped by category of exercise limitation

	N (n = 25)	LVD (n = 20)	PV (n = 25)	RL (n = 8)	p
Peak VO ₂ , % predicted	78.4 (64.3–103.4) [^]	58.1 (36.4–75)*	72.8 (50.8–110) [^]	53.8 (43.8–103)*	<0.001
Peak VO ₂ /HR, % predicted	84.1 (68.8–129)	72.6 (43.9–98)*	77.9 (57.1–119)*	64 (50–110)*	<0.001
Peak HR, % predicted	88.4 (61.1–100.7) [~]	80.4 (70.9–107.2) [~]	93.5 (81.7–122)	90 (84–94)	<0.001
SPO ₂ rest, %	98 (96–100)	98 (96–100)	98 (91–100)	96.5 (94–100)	0.330
SPO ₂ peak, %	97 (94–99) [#]	96.5 (93–100)	95 (81–99)	89 (82–98)	0.111
ΔSPO ₂ , %	1 (0–4) [#]	2 (0–5)	3 (0–17)	6 (1–17)	0.066
Peak V _E , l/min	39.8 (26.9–80.2)	35.8 (23.1–64.8)	42.2 (28.4–62.3)	44.1 (30–80.8)	0.052
VE/VCO ₂ @AT	32 (24–33) [#]	38 (27–62)*, [#]	38 (34–43)*, [#]	49.5 (34–80)*	<0.001
VE/VCO ₂ @peakVO ₂	32 (23–36) [#]	38 (26–73) [#] ,*	38 (33–42) [#] ,*	49 (34–80)*	<0.001
PETCO ₂ @AT	39 (26–47) [#]	35 (20–43) [#] ,*	35 (30–38) [#] ,*	29 (22–36)*	<0.001
PETCO ₂ @peakVO ₂	37 (31–49) [#] , [~]	34 (16–46) [#]	33 (30–40) [#]	26 (21–34) [~]	<0.001
Mean blood pressure peak, mm Hg	128.3 (106.7–166.7) [#]	123.3 (100–176.7)	137.5 (116.7–170) [#]	111.7 (106.7–136.7)	0.002
Mean blood pressure rest, mm Hg	96.7 (80–120)	101.7 (83.3–120)	102.5 (83.3–126.7)	95.8 (85–106.7)	0.168
BR, liters	47.8 (18–110) [#]	39.8 (23–118) [#]	36.4 (16–70) [#]	3.7 (0–11)	<0.001

p: for overall comparisons between the four groups. * p < 0.05 for comparisons between the N group and the other groups. [^] p < 0.05 for comparisons between the LVD group and the other groups. [~] p < 0.05 for comparisons between the PV group and the other groups. [#] p < 0.05 for comparisons between the RL group and the other groups.

or the N group. DLCOc % predicted was significantly higher among the N group compared to either the RL or the LVD group; however, DLCOc % predicted was abnormally reduced (<80% predicted) among all SSc patients. FEV₁/FVC ratio and KCOc were the least discriminative variables, since they were similar across all four groups. Imaging data came to an agreement with functional RL; 75% of the RL patients presented with extended pulmonary fibrosis on HRCT, compared to 15% of the patients within N group and 8% of those with PV; surprisingly 40% of the LVD patients also presented with extensive pulmonary fibrosis (table 2).

Regarding the rest of the baseline data, the resting sPAP values carried some discriminatory information – with patients in the N group presenting with significantly lower values compared to the rest; while age, BMI and gender ratio were similar across the groups.

Exercise Characteristics according to Exercise Impairment Categorization

Exercise characteristics across the four groups are presented in tables 3 and 4. Apart from the obvious differences in variables which constructed the initial algorithm used to categorize exercise impairment, i.e. peak VO₂, AT, BR and VE/VCO₂@AT (fig. 1), several other parameters were found to be different across the categories of exercise limitation. Patients without evident heart or lung disease (the N group) presented with higher peak WR (% predicted) compared to those in the RL and LVD groups

and with higher peak VO₂/HR (% predicted), higher PETCO₂@AT and lower VE/VCO₂@peakVO₂ compared to those in all other groups.

Several exercise parameters could discriminate the RL patients from the other groups. VE/VCO₂@AT and VE/VCO₂@peakVO₂ were significantly higher, while PETCO₂@AT, PETCO₂@peakVO₂ and BR were significantly lower among the RL patients compared to all other groups (table 4). ΔPETCO₂ was negative among the patients in the RL group, discriminating them from either the N or LVD group. AT (% predicted), nadir SPO₂ and ΔSPO₂ were significantly different between the RL and N groups, while the mean blood pressure peak was significantly higher in both the N and PV groups compared to the RL group (tables 3, 4).

For patients in the PV group, PETCO₂ carried the most discriminative information. PETCO₂@peakVO₂ could discriminate the PV from either the N or the RL group, but it was not different to the values of patients with LVD. The change of PETCO₂ from rest to AT was even more informative, since negative ΔPETCO₂ values differentiated patients in the PV group from both the N and LVD groups. From the rest exercise measurements, peak HR (% predicted), AT (% predicted), peak VO₂ (% predicted) and peak WR (% predicted) were of great significance, since they could differentiate between the patients in the PV and LVD groups (table 4).

Patients with LVD presented with the worst exercise capacity. Peak WR (% predicted) and AT (% predicted)

were lower among the LVD patients compared to all other groups, although this difference reached statistical significance only for the N and the PV group. Peak $\dot{V}O_2$ (% predicted) could also differentiate the LVD group from either the N or PV group, but the values were similar between the LVD and RL groups. Furthermore, measures of ventilatory inefficiency during exercise, i.e. $PETCO_2$ and VE/VCO_2 , could differentiate the LVD group from either the N or RL group, while $\Delta PETCO_2$ discriminated the LVD from the PV group (tables 3, 4).

Discussion

This study indicated that during maximal CPET, SSc patients present with different patterns of gas exchange according to the specific cause of exercise limitation. Patients with normal or subnormal exercise capacity but without evident heart or lung disease (the N group) and those with RL were the groups most easily to discriminate, while in order to differentiate between the LVD and PV groups a combination of several resting and exercise measurements needs to be taken into consideration.

Almost one third of the patients with SSc presented with normal or subnormal exercise capacity. Apart from the reduced DLCOc (% predicted), which is a hallmark of scleroderma [24], the remaining pulmonary function measurements were normal; while most of these patients had limited fibrosis on HRCT and no signs of pulmonary hypertension on rest echocardiograph, as expected. Most of the studies in the field reported that the vast majority of patients with SSc presented with significant exercise limitation [8, 9, 11]. Disease severity could be one reason for this discrepancy, since CPET is used early in the functional evaluation of patients with SSc in our institution. Another reason might be that several patients categorized in the N group presented with subnormal exercise capacity due to deconditioning. Chronic inflammation, pain, musculoskeletal disease due to cutaneous lesions or arthritis, chronic anxiety and depression, social withdrawal or isolation due to disfigurement and potential adverse effects of corticosteroid use on emotional status and muscular function [25–27] are only some of the potential factors leading to decreased physical activity and increased exertional dyspnea among these patients, without evident heart or lung involvement being present.

Although RL is the least common cause of exercise impairment, it is the most obvious in terms of discrimination. These patients presented with a restrictive resting ventilatory pattern and extended fibrosis on HRCT. Sev-

eral CPET parameters were found to be significantly different, compared to other groups; however, the indices of ventilatory inefficiency and gas exchange abnormalities were the most important. Ventilation-perfusion mismatching, rapid shallow breathing and increased dead-space ventilation due to the parenchymal distortion and vascular destruction of the fibrotic lung are the probable causes of abnormal ventilatory response to exercise [7, 28], as established by a high VE/VCO_2 ratio, low $PETCO_2$, hypoxemia and negative $\Delta PETCO_2$ among patients with RL. Increased VE/VCO_2 and decreased $PETCO_2$ have been previously related to pulmonary vascular disease [12], which in our RL group mostly reflects loss of vascular bed due to pulmonary fibrosis, and were also found in exercising patients with idiopathic pulmonary fibrosis [28]. Interestingly, these patients presented with a marked impairment of exercise capacity, similar to patients with cardiac involvement. The majority of previous studies have mainly focused on circulatory impairment among patients with scleroderma, so published results regarding RL during maximal CPET are currently limited. However, the number of patients in this subgroup in our study is relatively small, so results should be interpreted with some caution.

PV was a frequent cause of exercise limitation, being present in more than one-third of SSc patients in our study. However, this category was not easy to differentiate based solely on the use of resting measurements. It has already been described that the development of pulmonary fibrosis is associated with increased pulmonary vascular resistance [28]; however, in patients with RL this is a concomitant disorder and not the primary cause of exercise limitation. Moreover, it is not unusual for patients with SSc-associated pulmonary arterial hypertension to present with concomitant primary or secondary left heart disease [29–31]; thus the utilization of CPET is necessary for the differentiation between the PV, RL and LVD groups. $PETCO_2$ reflects the ability of the cardiopulmonary system to discard excessive carbon dioxide produced during exercise. Low $PETCO_2$ values at peak exercise are a useful marker for the identification of pulmonary hypertension both in patients with heart failure [32] and interstitial lung disease [33]. Steady or increasing $PETCO_2$ values from rest to AT ($\Delta PETCO_2$) reflect an intact pulmonary circulation [7], a characteristic which discriminates PV from both the LVD and N groups in our study. Furthermore, all measures of exercise capacity, i.e. peak $\dot{V}O_2$ (% predicted), peak WR (% predicted) and AT (% predicted), as well as peak HR (% predicted), were significantly higher in the PV group compared to the LVD group. Nevertheless, maximum exercise capacity, as de-

scribed by peak VO_2 (% predicted) and peak WR (% predicted), was similar between the PV and N groups; this lack of difference indicates that other CPET variables, such as ΔPETCO_2 , might be more sensitive in detecting emerging abnormalities in pulmonary vasculature, before the establishment of functional impairment is evident.

In our study, LVD was the main cause of exercise limitation in approximately one quarter of the participants. Serum antibodies were significantly different among these patients, since anti-sclero70 antibodies were positive and ACA were negative for the vast majority of them suggesting diffuse SSc – the subtype of disease more commonly associated with myocardial fibrosis. Even though resting pulmonary variables were not as impaired as among the RL patients, the subjects with LVD had a restrictive lung function pattern, while extensive pulmonary fibrosis on HRCT was frequent among them, confirming previous findings of the association between pulmonary and myocardial fibrosis among SSc patients [34]. A low AT and VO_2 with positive ΔPETCO_2 discriminated them from the PV group, while an increased VE/VCO_2 , low PETCO_2 and high BR differentiated these patients from the RL group. Myocardial fibrosis resulting from repeated, focal, ischemic injury due to abnormal coronary vasoreactivity and impaired myocardial microcirculation is the hallmark of primary cardiac involvement in SSc [35]. Cardiac involvement is usually subclinical and underdiagnosed, due to the inability of conventional echocardiography to capture early changes in myocardial contractility and overall heart performance; thus most studies have shown a low prevalence of decreased left ventricular ejection fraction [36]. However, undetected cardiac abnormalities can silently progress to life-threatening arrhythmias or heart failure, and consequently a patient may present with advanced signs of heart failure and an ominous prognosis [4]. Thus, the utilization of other noninvasive assessments of cardiac involvement complementing the physician's clinical skills is highly encouraged, as it may lead to the initiation of specific therapy at a time when it is most likely to be effective. In that respect, the combined use of CPET variables and baseline characteristics for the identification of LVD as the main cause of exercise limitation at a preclinical stage may have an impact on disease prognosis.

The retrospective design of the study is subjective to the general bias of this type of studies; nevertheless, the prospective collection of the data has minimized recall bias. Unlike previous studies in the field, several patients presented with normal or subnormal exercise capacity, while the sample size is bigger; thus, the results are easier

to generalize to patients of various disease severity. Unfortunately, a discriminant analysis to identify the best predictor of exercise limitation in each group could not be conducted, due to the relatively small and variable number of patients included in each subcategory. The 6-min walking test, a submaximal exercise test previously used to evaluate functional capacity of SSc patients, was not conducted; nevertheless recent evidence has questioned its validity in patients with SSc when pulmonary involvement is present [37], so it is very unlikely that it would have added any more discriminating information. Cardiac catheterization, the gold standard method to diagnose PV, was not applied; however, it is an invasive technique and not applicable in everyday clinical practice. The use of pulse oximetry to evaluate oxygenation, instead of invasive arterial blood gas measurements, might also limit our study findings to some extent. Nevertheless, this approach was utilized to minimize patient discomfort, while it had been previously used among patients with SSc [12].

In conclusion, this study applied a CPET algorithm to estimate the prevalence and determine the potential causes of exercise impairment among patients with scleroderma. Since exertional dyspnea and reduced physical performance are common manifestations of SSc, phenotyping functional impairment could be particularly useful in the clinical evaluation of patients with SSc. This might be even more important for patients with either LVD or PV, for whom early identification and treatment of the specific disorder might alter the course of their disease. Our study indicates that the combined evaluation of baseline measurements with CPET variables could offer valuable information in that direction. Future prospective studies are needed in order for the impact of these noninvasive markers of functional capacity on SSc prognosis, in terms of specific and all-cause morbidity and mortality, to be further assessed.

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