Developing Pulmonary Vasculopathy in Systemic Sclerosis, Detected with Non-Invasive Cardiopulmonary Exercise Testing

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Abstract

**Background:** Patients with systemic sclerosis (SSc) may develop exercise intolerance due to musculoskeletal involvement, restrictive lung disease, left ventricular dysfunction, or pulmonary vasculopathy (PV). The latter is particularly important since it may lead to lethal pulmonary arterial hypertension (PAH). We hypothesized that abnormalities during cardiopulmonary exercise testing (CPET) in patients with SSc can identify PV leading to overt PAH.

**Methods:** Thirty SSc patients from the Harbor-UCLA Rheumatology clinic, not clinically suspected of having significant pulmonary vascular disease, were referred for this prospective study. Resting pulmonary function and exercise gas exchange were assessed, including peakVO2, anaerobic threshold (AT), heart rate-VO2 relationship (O2-pulse), exercise breathing reserve and parameters of ventilation-perfusion mismatching, as evidenced by elevated ventilatory equivalent for CO2 (VE/VCO2) and reduced end-tidal pCO2 (PETCO2) at the AT.

**Results:** Gas exchange patterns were abnormal in 16 pts with specific cardiopulmonary disease physiology: Eleven patients had findings consistent with PV, while five had findings consistent with left-ventricular dysfunction (LVD). Although both groups had low peak VO2 and AT, a higher VE/VCO2 at AT and decreasing PETCO2 during early exercise distinguished PV from LVD.

**Conclusions:** Previously undiagnosed exercise impairments due to LVD or PV were common in our SSc patients. Cardiopulmonary exercise testing may help to differentiate and detect these disorders early in patients with SSc.

Introduction

Dyspnea on exertion, fatigue, and reduced exercise tolerance are common symptoms in patients with systemic sclerosis (SSc). These symptoms can often be explained by involvement of the musculoskeletal system, lungs, heart, chest wall, and/or pulmonary vasculature, in isolation or combination. Patients with SSc are at particular risk for developing pulmonary vasculopathy (PV) leading to pulmonary arterial hypertension (PAH). Untreated, PAH results in right ventricular failure, and early death [1].

PV impairs dilatation of affected pulmonary blood vessels, impeding pulmonary blood flow during exercise. This eventually leads to pulmonary hypertension and exercise intolerance. Initially, the degree of exercise limitation is determined by the ability of the right ventricle to hypertrophy and maintain adequate blood flow through the lungs. At this stage, pulmonary hypertension might only be visible during exercise [2,3]. Over time, vasculopathy progresses and the right ventricular reserve fails to meet the pulmonary blood flow required for the increased O2 demand of exercise, leading to exertional dyspnea and fatigue and physical signs of pulmonary hypertension.

Early detection of PV may be desirable since timely therapeutic intervention improves outcomes in experimental models [4,5]. Additionally, treatment of patients with early PAH can delay clinical worsening [6]. Pulmonary vasculopathy develops unevenly in the lungs. Thus, abnormal gas exchange findings characteristic of ventilation-perfusion mismatching, is an early abnormality during cardiopulmonary exercise testing (CPET) [7].

The gas exchange abnormalities during CPET in patients with PV reflect hypoventilation of well-ventilated acini. Thus, ventilation...
(VE) is high compared to relatively low CO₂ output (VCO₂) and reduced end-tidal PCO₂ (P_{ET}CO₂), manifesting hypoperfusion of well-ventilated lung. In this study, we performed CPET in a group of referred SSc patients, without previously known or suspected PV. We expected that these patients would display heterogeneous gas exchange patterns during exercise, which cannot be explained by resting measurements alone. We hypothesized that we would find characteristic gas exchange patterns that would enable us to discriminate between the different causes of exercise intolerance, based on the exercise pathophysiology. We hypothesized that some of the patients would show gas exchange patterns during exercise that are characteristically found in patients with overt pulmonary vascular pathophysiology.

Methods

Ethics statement

This study was conducted in accordance with Good Clinical Practices and the current version of the revised Declaration of Helsinki [8]. The local Los Angeles Biomedical Research Institutional Review Board approved the protocol. A written informed consent was obtained from each patient prior to enrollment.

Study population

We prospectively screened 32 SSc patients referred from the Rheumatology Clinic at Harbor-UCLA Medical Center for CPET in order to determine if they had evidence of PV. Prior to referral, all patients had chest X-rays and/or high-resolution chest CT-scans. All patients had echocardiography with estimation of pulmonary artery pressure (PAP) prior to referral. Patients with estimated systolic PAP >35 mmHg, were excluded.

All patients had been diagnosed with SSC according to the criteria of the American College of Rheumatology (ACR) [9]. One patient refused to perform CPET and another could not perform CPET because of joint stiffness. Thus, thirty patients performed CPET.

Evaluations

6-minute walk test. All patients performed an unencouraged, standardized 6-minute walk test (6MWD), at least one hour before or after CPET [10].

Pulmonary function testing. Total lung capacity (TLC), forced vital capacity (FVC), forced expired volume in one second (FEV₁), diffusing capacity for carbon monoxide (DL_{CO}) and alveolar volume (VA) were all measured as part of CPET and are expressed as percent predicted.

Assessment of restrictive lung disease. Restrictive lung disease was assessed by a combination of resting pulmonary function tests (PFTs), including diffusion capacity for carbon monoxide (DL_{CO}), by Chest X-ray (CXR) and by high-resolution computed tomography (HRCT). An HRCT was performed if there were abnormalities in PFTs or CXR. An HRCT was not performed in patients with normal PFTs and a normal CXR, or a definite diagnosis of ILD based on these two measurements.

The available HRCT-scans in patients with suspected ILD (20 out of 30) were analyzed for signs of pulmonary venous occlusive disease (PVOD). Main characteristics were enlarged mediastinal lymph nodes, alveolar hemorrhage, centrilobular ground glass opacities and septal lines on HRCT.

Cardiopulmonary exercise testing. CPET was performed with upright cycling on a stationary cycle ergometer. The exercise protocol consisted of 3 minutes of rest and 3 minutes of unloaded cycling, followed by an incremental work rate between 5 and 15 watts per minute up to the patients’ maximum tolerance, then 3 minutes of recovery. Gas exchange was measured breath-by-breath during the test, using a MedGraphics CPX-Ultima gas exchange system (Medical Graphics Corporation, St. Paul, Minnesota). Equipment was calibrated as previously described [11]. ECG and pulse oximetry were continuously monitored and blood pressure was measured every two minutes. Minute ventilation (VE), heart rate (HR), VO₂/HR, VO₂, VCO₂, VCO₂ vs VO₂, VE/VO₂, VE/VCO₂, tidal volume (VT) vs VE, end-tidal PO₂ (P_{ET}O₂) and PCO₂ (P_{ET}CO₂) and the respiratory exchange ratio (RER) were averaged every 10 seconds. The anaerobic threshold (AT) was determined from gas exchange, by the V-slope method as previously described [12], in all patients. The AT was derived from a plot with VO₂ (x-axis) and VCO₂ (y-axis) on equal axis scaling, and was recognized as the point where VCO₂ started to increase faster than VO₂. AT prediction was performed as previously described [13,14]. The other key variables were calculated and plotted as previously described [15,16]. All studies were independently reviewed by two authors (DD and KW). Disagreements were adjudicated after review by a third author (JH), and consensus agreement among all three.

Categorizing Exercise Impairment

Patients with known severe heart or lung disease limiting exercise, or individuals with known PAH, were not referred by the Rheumatologists. An additional two patients with uninterpretable cardiopulmonary exercise test results were not included in the analysis (2 of 30 patients). The first patient stopped during the unloaded cycling phase due to joint pain. The second patient had a very noisy and chaotic breathing pattern. For both of these patients, peak VO₂, the AT and VE/VCO₂ at the AT could not be accurately determined. Thus, 28 patients were available for analysis. Figure 1 presents the algorithm utilized. Disagreement in the blinded interpretation of the CPET studies occurred in 2 of 28 interpretable cases. Agreement was reached in these two cases by review of a third author. The normal category included those with a normal peak VO₂, normal anaerobic threshold (AT) normal ventilation-perfusion matching, and no exercise-induced hypoxemia (6 of 28 patients). The normal category also included six patients with a reduced peak VO₂, but with normal AT, no abnormality in ventilation-perfusion matching or exercise-induced hypoxemia and an RER at peak exercise below 1.0, indicating submaximal effort. These patients were categorized as not being limited by heart or lung disease. Thus, 12 of the 28 patients were categorized as normal.

Patients were categorized in the left ventricular dysfunction (LVD) group if they had a reduced peak VO₂, AT, peak O₂-pulse and Δ VO₂/ΔWR - but without ventilation-perfusion mismatch or exercise-induced hypoxemia or RER at peak exercise <1.0. (5 of 28 patients were in this category).

Patients were categorized in the PV group if they had a reduced peak VO₂ and AT, reduced peak O₂-pulse and Δ VO₂/ΔWR, and ventilation-perfusion mismatch (elevated VE/VCO₂ at the AT or at the ventilatory compensation point (VCP) following AT). In addition, based on prior research [17,18], suspected PV was separated from LVD by a decreasing P_{ET}CO₂ from the start of exercise to AT (9 of 28 patients were in this category), in contrast to an increasing P_{ET}CO₂ in LVD and normal subjects. Two other patients showed rising P_{ET}CO₂ during exercise but were classified as suspected PV secondary to their restrictive lung disease with parallel loss of pulmonary capillary volume [low TLC and DLCO with normal FEV₁/FVC], however breathing reserve was thought to be adequate without mechanical ventilatory limitation at peak exercise. This is based on a prior study [19] showing that lung...
Statistical analysis
A total of 28 of the SSc patients referred, with interpretable CPET studies, were analyzed; they were divided into 3 major categories: normal, LVD and PV, as described above. Continuous variables are expressed as mean ± SD. The three groups were individually compared to each other. Differences were analyzed using one way ANOVA, followed by Holm-Sidak testing for multiple comparisons. Nominal data were analyzed by Chi-square test for multiple groups. In all cases, a p value <0.05 was considered statistically significant.

Results
Table 1 shows the demographics according to diagnostic category. All patients tolerated CPET well, and there were no adverse events.

Gas Exchange Patterns
Figure 2 shows how the 15 variables taken from the CPET 9-panel plots of two representative SSc patients were analyzed. Figure 2a shows an SSc patient with a normal CPET response; Figure 2b shows another SSc patient with PV. The 4 arrows in Figures 2a and 2b correspond to the 4 branch-point parameters shown in Figure 1. The legend for figure 2 provides further detail.

Table 2 shows the 6 minute walk distance, key pulmonary function measurements, the presence of restrictive lung disease, pulse oximetry, and seven CPET parameters by diagnostic categories. Six patients achieved their predicted peak VO2, and another six stopped exercise prematurely without evidence of cardiovascular or pulmonary limitation. All 12 had linear increases in HR vs VO2 relationship towards their predicted value, normal AT, O2-pulse, and VE/VCO2 @ AT, as exemplified in figure 2a. We classified all 12 as normal. The other 16 patients achieved a symptom-limited test below their predicted peak VO2, and also had additional abnormalities. Of these 16, 5 were classified as LVD and 11 were classified as PV. Two of the latter also had significant restrictive lung disease with reduced FVC, TLC and DLCO. No patients were limited by obstructive lung disease, all had an adequate breathing reserve at peak exercise. In the patients who underwent HRCT due to clinical suspicion of interstitial lung disease (ILD), presence of ILD was found among all groups, with a trend to higher occurrence in the PV group. However, this difference did not reach statistical significance (p = 0.07).

None of these patients showed signs of PVOD.
Table 1. Demographics for each exercise diagnosis in 30 scleroderma patients.

|                           | Not interpretable exercise test results (n = 2) | Normal exercise capacity (NL) (n = 12) | Left Ventricular Dysfunction (LVD) (n = 5) | Pulmonary vasculopathy (PV) (n = 11) | NL vs. LVD | p-value NL vs. PV | LVD vs. PV |
|---------------------------|-------------------------------------------------|----------------------------------------|--------------------------------------------|-------------------------------------|------------|-------------------|----------|
| M/F                       | 0/2                                             | 2/10                                   | 2/3                                        | 1/10                                |            |                   |          |
| Limited/diffuse SSc       | 2/0                                             | 9/3                                    | 3/2                                        | 9/2                                 |            |                   |          |
| NYHA Class I              | 1/2                                             | 6/12                                   | 4/5                                        | 2/11                                |            |                   |          |
| NYHA Class II             | 1/2                                             | 6/12                                   | 1/5                                        | 8/11                                |            |                   |          |
| NYHA Class III            | 0/2                                             | 0/12                                   | 0/5                                        | 1/11                                |            |                   |          |
| Age (years)               | 51 ± 1                                          | 52 ± 7                                 | 41 ± 11                                    | 49 ± 14                             | n/s (p = 0.31) |                   |          |
| BMI (kg/m²)               | 28.2 ± 7.2                                      | 28.5 ± 7.7                            | 27.0 ± 3.9                                 | 26.4 ± 5.7                          | n/s (p = 0.73) |                   |          |
| ACA positive              | 1/2                                             | 5/12                                   | 2/5                                        | 2/11                                |            |                   |          |
| Scl-70 positive           | 1/2                                             | 3/12                                   | 0/5                                        | 3/11                                | n/s (p = 0.30) |                   |          |

ACA = anti-centromer antibodies.
Scl-70 = DNA-topoisomerase I antibodies.
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Figure 2. Gas exchange response to exercise in two SSc patients. Nine panel plots of a patient with normal exercise performance (Fig. 2a) and one with pulmonary vasculopathy (Fig. 2b). The protocol consisted of a 3-minute resting period, followed by 3 minutes of very-low-level cycle exercise, and then increasing cycle workload to the patient’s maximum tolerance. Points are 20-second averages. Panel 1 is plot of ventilation against time. Panel 2 is plot of heart rate and O₂-pulse against time. Panel 3 is plot of O₂ uptake (VO₂), CO₂ output (VCO₂) and work rate against time. Panel 4 is plot of minute ventilation (VE) against VCO₂. Panel 5 is plot of VCO₂ and HR against VO₂. Panel 6 is plot of ventilatory equivalent for VO₂ (VE/VO₂) and VCO₂ (VE/VCO₂) against time. Panel 7 is plot of tidal volume against minute ventilation, with resting maximum voluntary ventilation on the X-axis and inspiratory capacity and vital capacity, measured at rest, on the Y-axis. Panel 8 is plot of gas exchange ratio (RER) against time. Panel 9 is plot of end tidal pO₂ (PETO₂), end tidal pCO₂ (PETCO₂) and pulse oximeter arterial oxyhemoglobin saturation against time. The normal subject (figure 2a) is a 59 year old female with scleroderma. Peak VO₂ and AT are normal (panels 3 and 5). There are no signs of impaired oxygen flow, or ventilation/perfusion mismatching during exercise. Peripheral oxyhemoglobin saturation does not decrease during exercise. There is adequate breathing reserve. The subject with suspected pulmonary vasculopathy (figure 2b) is a 37 year old female with scleroderma. Peak VO₂ and AT are reduced (panel 3, panels 3 and 5). Ventilatory equivalents are elevated and decrease only slightly during exercise (panel 6). End-tidal pCO₂ is low and decreases during exercise (panel 9), consistent with reduced gas exchange efficiency rather than voluntary hyperventilation (RER is normal, panel 8). The patient stopped exercise because of leg pain. Four arrows are placed on each of Figures 2a and 2b that correspond to the branch-points described in Figure 1. Arrow 1 points to the peak VO₂ in panel 3 (branch-point 1). Arrow 2 points to the AT in panel 5 (branch-point 2). Arrow 3 points to the VE/VCO₂ at the AT in panel 6 (branch-point 3). Arrow 4 points to the changing P(T)CO₂ from start of exercise to AT in panel 9.
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Exercise Capacity

The cause of exercise limitation discerned from all 28 interpretable cardiopulmonary exercise tests was determined using the algorithm shown in Figure 1. Its branch-points systematically examined each of the key parameters from the 9-panel plots (Figure 2). Figure 2 shows where the branch-point data were obtained in each patient’s 9-panel plot. Exercise capacity was significantly reduced due to identifiable defects in 16 of the 28 patients. In these patients, peak VO₂ and VO₂ at AT were <75% of the absolute predicted value and/or oxygen pulse reached a plateau at a significantly reduced value above the AT (Figure 2b, panel 2).

Several measurements in Table 2 are of special interest. FVC values were markedly reduced, 6MWD was moderately reduced, and DLCO values were markedly reduced from normal in the PV patients. In these patients, peak VO₂ and VO₂ at AT were significantly reduced due to identifiable defects in 16 of the 28 patients. In these patients, peak VO₂ and VO₂ at AT were <75% of the absolute predicted value and/or oxygen pulse reached a plateau at a significantly reduced value above the AT (Figure 2b, panel 2).

As single parameters, only PETCO₂@AT (p = 0.004), VE/VCO₂@AT (p = 0.002) and the changes in PETCO₂ from early exercise to the AT (p = 0.002) distinguished LVD from PV. The directional change in PETCO₂ at the start of exercise to the AT (ΔPETCO₂) tends to be negative (decreases to the AT), as has been previously shown in patients with idiopathic PAH [17,18]. In contrast, PETCO₂ increases from the start of exercise to the AT in the normal subjects and the patients with LVD (Fig. 3). There was no significant difference between the normal subjects and the patients with LVD (Fig. 3). There was no significant difference between the normal (3.2 ± 2.3 mm Hg) and LVD (3.9 ± 2.0) groups (p = 0.93) in the PETCO₂ change. However, the PET group (−1.3 ± 2.6) differed significantly from both (p < 0.001 and p = 0.002, respectively).

Figure 4 shows the relationships of PETCO₂ to VE/VCO₂ at the AT of all patients. Although there is some overlap, most patients with pulmonary vasculopathy had a lower PETCO₂ and higher VE/VCO₂ than the normal and LVD groups.

The FEV₁/FVC ratio showed the same results: Only the normal and the PV group showed a difference which reached statistical significance (p = 0.01). The difference between the normal and the LVD group, as well as the difference between the PV and the LVD group were not statistically significant (p = 0.17 and p = 0.37, respectively).

Peak VO₂ at AT, peak O₂ pulse and Δ VO₂/ΔWR were all reduced in patients with PV and LVD, but the magnitudes and patterns of these reductions did not distinguish the two disorders. As single parameters, only PETCO₂@AT (p = 0.004), VE/VCO₂@AT (p = 0.002) and the changes in PETCO₂ from early exercise to the AT (p = 0.002) distinguished LVD from PV.
Discussion

Previous studies have described lung gas exchange abnormalities at rest and during exercise in SSc patients [20]. However, this is the first study to show that abnormal gas exchange patterns during exercise, characteristic of PV, can be seen in patients with SSc without elevated pulmonary artery pressure on echocardiography or of having pulmonary vascular disease based on clinical
suspicion. These abnormal CPET patterns may represent early PV, which with time, may lead to clinical and symptomatic pulmonary hypertension at rest.

Using CPET, we found evidence of possible PV in an SSc patient population, which was asymptomatic for the disease. A decreased peak VO₂ along with a reduced AT has been the primary marker of reduced exercise capacity in patients with cardiovascular limitations to exercise [21]. However, patients with multi-organ diseases like scleroderma, are frequently exercise-limited with unclear cause. The 6MWD cannot be expected to define pathophysiology or differentiate causes of reduced exercise capacity. Therefore assessment of measures beyond 6MWD and peak VO₂ measurements is needed to identify the specific pathophysiology underlying exercise intolerance.

In this study, we hypothesized that measures of ventilatory efficiency, specifically PETCO₂ and VE/VCO₂ and their patterns of change during exercise, added to other gas exchange measures evaluating peak and sustainable cardiac output, or VO₂, could be used to differentiate patterns which indicate possible PV from other causes of exercise gas exchange abnormalities. Elevated VE/
VE/VCO₂ is increased, the degree depending on disease severity. The additional finding of a low PETCO₂ at the AT was even more discriminatory when used to differentiate early LVD from early PV (Table 2). Because of loss of perfusion to ventilated lung, there is less CO₂ laden blood to release CO₂ to the airspaces for a given ventilation in patients with suspected PV. Thus, to eliminate the metabolic CO₂, ventilation must increase resulting in an elevated ratio of VE to VCO₂. In left ventricular failure, it is also common for portions of the lung to be well-ventilated, but be poorly perfused. Thus, VE/VCO₂ is commonly used as an index of the severity of LVD [22,23]. Due to its pathogenesis, VE/VCO₂ should invariably be increased in patients with PV [18,24,25]. Because of the loss of vascularity to lung acini, PETO₂ is diluted in proportion to the fraction of underperfused acini. Thus, PETCO₂ is decreased as VE/VCO₂ is increased, the degree depending on disease severity. In less severe stages of pulmonary vascular disease, small increases in VE/VCO₂ are accompanied by large decreases in PETCO₂ [18] (Figure 4). Thus, a reduced PETCO₂ at the AT or VCP is a valuable marker of blood vessel loss, and may be sensitive in detecting early pulmonary vascular disease.

It has also been shown, in the transition from the start of exercise to the AT, that PETCO₂ decreases to decrease in PAH, whereas the PETCO₂ tends to increase in LVD [17]. This observation appears to occur in SSC patients with suspected PV as well. Figure 5 relates the degree of lung restriction (reduced FVC) to the elevation of VE/VCO₂ (Fig. 5a) and dilution of PCO₂ (Fig. 5b) at the AT or VCP. All three groups had reductions in FVC, but it is mainly the PV group that had the abnormally high VE/VCO₂ and low PETCO₂ values. This might become therapeutically relevant in patients with SSC and borderline pulmonary hypertension. Presumably, the best candidates for specific therapy would be those patients with the highest VE/VCO₂ and lowest PETCO₂ values and least lung restriction. However, the validation of this hypothesis is subject to further studies.

Study limitations

Our diagnostic algorithm categorizing exercise pathophysiology, based on patterns of exercise gas exchange, was designed to identify scleroderma patients with characteristic patterns of PV and normal pulmonary artery pressure on echocardiography. We did not perform right-heart catheterization in our patients, as the study aim was to detect patterns of early PV in patients who might not have yet progressed to clinical resting pulmonary hypertension, so that an elevated PAP during a resting right heart catheterization might not have yet progressed to clinical resting pulmonary hypertension: application of a registry approach. Ann Rheum Dis 62: 1081–1093.

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