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Predictors of Exercise-Induced Oxygen Desaturation in Systemic Sclerosis Patients With Interstitial Lung Disease

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BACKGROUND: The diffusion capacity of the lung for carbon monoxide (D_{LCO}) is a good marker of disease severity in patients with idiopathic interstitial pneumonia, and is associated with oxygen saturation; however, little is known about D_{LCO} in systemic sclerosis patients with interstitial lung disease. We studied potential predictors of exercise-induced oxygen desaturation in patients with systemic sclerosis. METHODS: Data were collected prospectively from 80 of 110 consecutive systemic sclerosis patients with normal oxygen saturation (> 95%) at rest, who could perform the 6-min walk test without physical discomfort, including leg pain. Pulmonary function tests and echocardiography were collected from all subjects. RESULTS: Thirty subjects showed a ≥ 4% decline in oxygen saturation during the 6-min walk test (desaturation group). The other subjects were assigned to the normoxic group. The percent-of-predicted values for FVC, FEV_1, total lung capacity, D_{LCO}, and D_{LCO}/alveolar volume were lower, and FEV_1/FVC was higher, in the desaturation group. Logistic regression analysis showed the percent-of-predicted D_{LCO} as a highly accurate predictor of exercise-induced oxygen desaturation: the area under the receiver operating characteristic curve was 0.92 (cutoff point 56.3%, sensitivity 0.83, specificity 0.86). Five subjects over the cutoff point of the percent-of-predicted D_{LCO} in the desaturation group could not be distinguished from the normoxic subjects with the lung-volume measurements or right-ventricular systolic pressure. CONCLUSIONS: The factor underlying exercise-induced oxygen desaturation appeared to be reduced percent-of-predicted D_{LCO}, which was useful as a predictor in over 80% of the subjects. *Key words: systemic sclerosis; interstitial lung disease; oxygen saturation; pulmonary function; pulmonary arterial hypertension; 6-min walk test.* [Respir Care 2014;59(1):75–80. © 2014 Daedalus Enterprises]

Introduction

Exercise-induced oxygen desaturation in patients with interstitial lung disease may be one of the crucial factors in exercise limitation. An S_{pO_2} decrease to ≤ 88% during the 6-min walk test (6MWT) predicts high mortality risk in patients with idiopathic interstitial pneumonia.[1] Oxygen desaturation during 6MWT correlates with the diffusion capacity of the lung for carbon monoxide (D_{LCO}).[2,3] Impaired D_{LCO} and pulmonary arterial hypertension are also found in patients with systemic sclerosis,[4,5] and low D_{LCO} (≤ 50%) was one of the predictors of death.[6] However, S_{pO_2} decrease of ≥ 4% during 6MWT correlates with age, dyspnea index, positive anti-Scl-70 autoantibody, and FVC, but D_{LCO} has not been examined in relation to oxygen saturation in patients with systemic sclerosis.[7]

Identifying predictors of exercise-induced oxygen desaturation would help to select patients who might benefit from additional monitoring using oximetry during 6MWT when oxygen saturation is normal at rest. Moreover, the suggestion of cutoff points for these predictors would help

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The authors have disclosed no conflict of interest.

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alert patients to avoid hypoxic risk.[8] In the present study we used 6MWT as a submaximal exercise to prospectively identify predictors of exercise-induced oxygen desaturation in patients with systemic sclerosis and interstitial lung disease.

Methods

The study was approved by the ethics committee of Kanazawa University Hospital, Kanazawa, Japan, and all subjects gave written informed consent. Between 2008 and 2012, 110 consecutive adult patients with systemic sclerosis and interstitial lung disease were referred to the Division of Rehabilitation Medicine, Kanazawa University Hospital. Interstitial lung disease was diagnosed via pulmonary function tests, high-resolution computed tomography, and/or open lung biopsy. The main reasons for the patients' visits were for the evaluation and rehabilitation treatment of digit ulcers, joint contracture, and exercise intolerance.

6MWT was conducted if S_{pO_2} was > 95% at rest on room air. The exclusion criteria were pain in or ulcers on the foot, severe cough, heart failure, or back pain. We enrolled 80 subjects (66 female, 14 male), with a mean age of 57.4 years (Fig. 1). During the 6MWT S_{pO_2} was monitored with a handheld pulse oximeter, with a reflectance sensor on the forehead, and was also measured at rest and at the end of the walk, without interfering with the 6MWT.

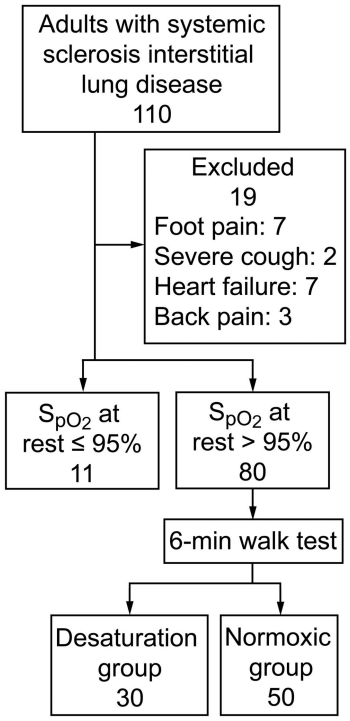

Fig. 1. Flow chart.

QUICK LOOK

Current knowledge

The diffusion capacity of the lung for carbon monoxide (D_{LCO}) is a good marker of disease severity in patients with idiopathic interstitial pneumonia, and is directly associated with a diminished oxygen saturation. The role of D_{LCO} in characterizing interstitial lung disease in patients with systemic sclerosis is not known.

What this paper contributes to our knowledge

Reduced D_{LCO} and percent-of-predicted lung volumes affected oxygen saturation during the 6-min walk test in patients with systemic sclerosis and interstitial lung disease. Percent-of-predicted D_{LCO} was a sensitive and specific predictor of exercise-induced oxygen desaturation.

We did not use a fingertip oximetry sensor because digit circulation is often deteriorated in patients with systemic sclerosis, which makes fingertip S_{pO_2} readings inaccurate.[9]

We measured percent-of-predicted FVC, FEV_1, FEV_1/FVC, total lung capacity (TLC), peak expiratory flow (PEF), residual volume/TLC (RV/TLC), D_{LCO}, and D_{LCO}/alveolar volume (D_{LCO}/V_A) (Chestac-9800, Chest Medical Instruments, Tokyo, Japan). Each predicted value was calculated with sex, age, and height[10] (per the Baldwin formula). Single-breath D_{LCO} was adjusted by hemoglobin concentration, according to the Cotes equation.[2]

Transthoracic echocardiography (iE33, Philips Healthcare, Best, Netherlands) was performed with the subject in the left-lateral decubitus position. Left-ventricular end-diastolic and end-systolic diameters were determined with M-mode echocardiography, and left-ventricular ejection fraction was calculated with the modified Simpson formula. Right-ventricular systolic pressure (RVSP), reflecting systolic pulmonary artery pressure, was estimated from the tricuspid regurgitating velocity, following the Bernoulli principle, via tissue Doppler echocardiography.[11,12]

Statistics

Subjects whose S_{pO_2} decreased ≥ 4% during 6MWT were assigned to the desaturation group, because exercise desaturation of ≥ 4% predicts mortality[1] and is an adverse prognostic sign[13] in patients with idiopathic pulmonary fibrosis. The remaining subjects constituted the normoxic group. Differences between the 2 groups were calculated with the 2-tailed *t* test. The chi-square test was used to compare sex distribution and skin-involvement subsets (diffuse versus limited type). Logistic regression was used

Table. Subjects

	All Subjects $n = 80$	Normoxic Subjects $n = 50$	Desaturation Subjects $n = 30$	P
Female/male, no.	66/14	43/7	23/7	.29
Age, y	57.4 ± 11.8	57.6 ± 12.3	57.0 ± 11.0	.80
Duration of disease, y	6.6 ± 7.9	6.4 ± 8.5	7.0 ± 7.0	.73
Skin involvement subset, no.				.055
Diffuse	45	24	21	
Limited	35	26	9	
FVC, % predicted	94.0 ± 22.9	103.3 ± 21.4	78.5 ± 18.3	< .001
FEV_1, % predicted	93.9 ± 24.0	101.2 ± 22.4	81.8 ± 21.8	< .001
FEV_1/FVC	79.9 ± 8.2	78.3 ± 8.5	82.5 ± 7.0	.02
PEF, % predicted	87.5 ± 16.5	88.2 ± 18.4	86.3 ± 15.6	.61
TLC, % predicted	85.9 ± 20.4	95.1 ± 16.3	70.5 ± 17.1	< .001
RV/TLC, %	95.5 ± 15.7	97.1 ± 14.7	92.9 ± 17.3	.28
D_{LCO}, mL/min/mm Hg	13.8 ± 4.5	16.0 ± 3.7	10.3 ± 3.2	< .001
D_{LCO}, % predicted	62.6 ± 19.5	72.7 ± 15.7	45.8 ± 12.4	< .001
D_{LCO}/V_A, mL/min/mm Hg/L	4.44 ± 1.13	4.68 ± 0.98	4.06 ± 1.28	.03
D_{LCO}/V_A, % predicted	84.9 ± 19.9	89.9 ± 17.6	76.2 ± 21.1	.005
LVEF, %	72.1 ± 4.7	72.4 ± 5.2	71.6 ± 3.9	.43
RVSP, mm Hg	31.1 ± 9.8	29.8 ± 8.2	33.2 ± 11.9	.18
6MWD, m	492 ± 102	504 ± 93	472 ± 115	.21

Values are means ± SD unless otherwise indicated.
PEF = peak expiratory flow
TLC = total lung capacity
RV = residual volume
D_{LCO} = diffusion capacity of the lung for carbon monoxide
V_A = alveolar volume
LVEF = left-ventricular ejection fraction
RVSP = right-ventricular systolic pressure
6MWD = 6-min walk distance

for parameters regarding exercise-induced oxygen desaturation; then, for parameters with high accuracy (indicated by the area under the receiver operating characteristic curve), sensitivity and specificity were obtained from critical points on the receiver operating characteristic curve. Moreover, all subjects were divided by degree of impairment in percent-of-predicted D_{LCO}, and lung volumes and RVSP were compared between the 2 D_{LCO} groups with the 2-tailed t test. Statistical analyses were performed with statistics software (JMP8.0, SAS Institute, Cary, North Carolina), except for the 95% CI for the area under the receiver operating characteristic curve, which was calculated with SPSS 17.0 (SPSS, Chicago, Illinois). In all analyses, $P < .05$ was taken to indicate significance.

Results

The Table describes the subjects. There were no differences in sex distribution, age, skin-involvement subset, duration of disease after the onset of Raynaud phenomenon, percent-of-predicted RV/TLC, percent-of-predicted PEF, left-ventricular ejection fraction, RVSP, or 6MWT distance between the desaturation and normoxic groups. The desaturation group had significantly lower percent-of-predicted FVC, FEV_1, TLC, D_{LCO}, percent-of-predicted D_{LCO}, D_{LCO}/V_A, and percent-of-predicted D_{LCO}/V_A, and significantly higher FEV_1/FVC.

In the logistic regression analysis, percent-of-predicted D_{LCO} was the most accurate predictor: area under the receiver operating characteristic curve 0.92 (Fig. 2). At the critical point on the receiver operating characteristic curve, the percent-of-predicted D_{LCO} was 56.3% (sensitivity 0.83, specificity 0.86). When the cutoff point for percent-of-predicted D_{LCO} was set at 56.3% for exercise-induced oxygen desaturation, 5 subjects in the desaturation group had percent-of-predicted $D_{LCO} > 56.3\%$, defined as the false negative subjects.

All subjects were classified per the percent-of-predicted D_{LCO} cutoff point, and then the percent-of-predicted FVC, FEV_1, TLC, and RVSP values of the 2 groups were compared (Fig. 3). The percent-of-predicted FVC, FEV_1, and TLC values in the desaturation group over the cutoff

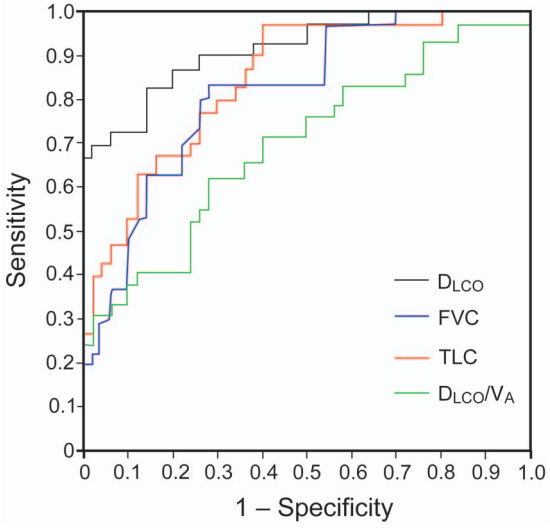

Fig. 2. Receiver operating characteristic curves for parameters affecting oxygen saturation during 6-min walk test. D_{LCO} = diffusion capacity of the lung for carbon monoxide. TLC = total lung capacity. V_A = alveolar volume. The area under the receiver operating characteristic curves were 0.92 (95% CI 0.85–0.98) for percent-of-predicted D_{LCO}, 0.82 (95% CI 0.73–0.91) for percent-of-predicted FVC, 0.84 (95% CI 0.76–0.93) for percent-of-predicted TLC, and 0.70 (0.57–0.82) for percent-of-predicted D_{LCO}/V_A.

point were significantly lower than those in the normoxic group. There was no significant difference in RVSP between the 2 groups. However, 5 false negative subjects showed low values for 3 lung volume parameters, and the range of values of false negative subjects overlapped with that of subjects in the normoxic group. Therefore, it was difficult to predictively distinguish them from subjects in the normoxic group using lung volume parameters, even after classification for percent-of-predicted D_{LCO} impairment.

Discussion

Significantly impaired D_{LCO}, FVC, FEV_1, and TLC were found in the desaturation group. Little information has been obtained on the correlation between lung parameters and exercise-induced oxygen desaturation in systemic sclerosis, though FVC previously showed a significant association with induced oxygen desaturation during 6MWT.[7] Percent-of-predicted D_{LCO} has been reported to be a predictor of 6MWT distance in patients with systemic sclerosis and interstitial lung disease.[4] Exercise-induced oxygen desaturation in patients with idiopathic interstitial pneumonia correlates with walk velocity, percent-of-predicted D_{LCO} and arterial oxygen pressure,[14] percent-of-predicted D_{LCO} and pulmonary capillary blood volume,[3] and D_{LCO}.[2] In support of those studies,

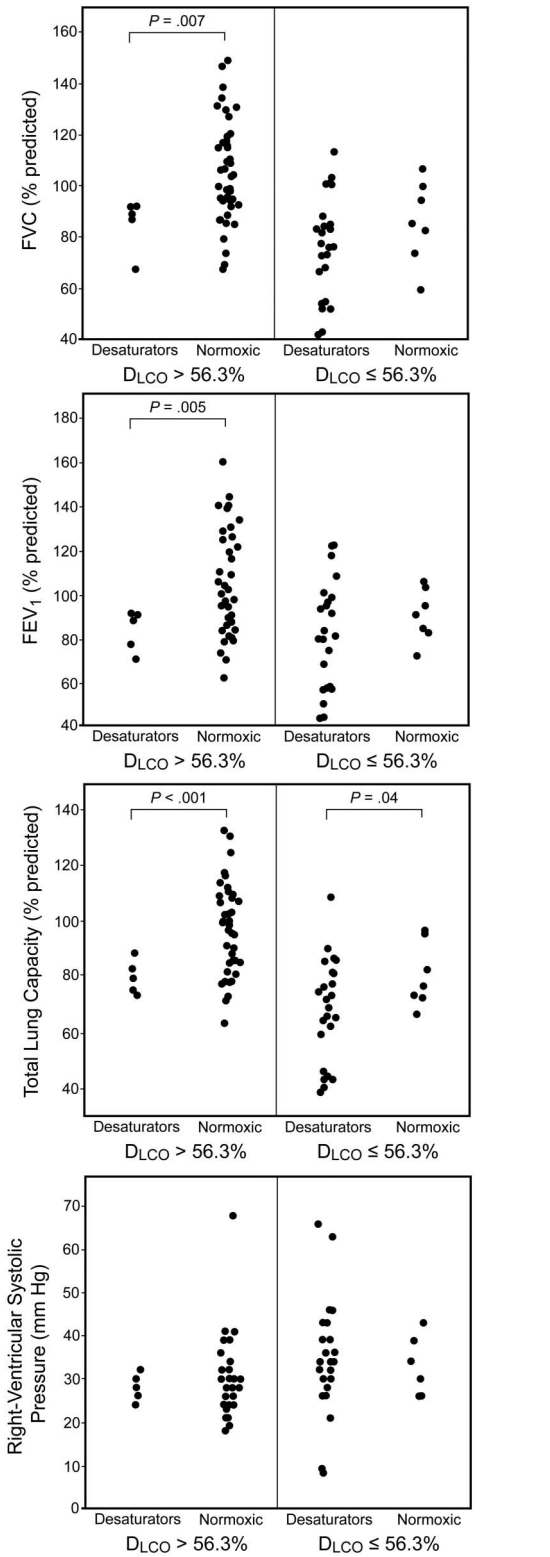

Fig. 3. Percent-of-predicted FVC, percent-of-predicted FEV_1, percent-of-predicted total lung capacity (TLC), and right-ventricular systolic pressure in 80 subjects classified according to degree of impairment in diffusion capacity of the lung for carbon monoxide (D_{LCO}), and according to desaturation (S_{pO_2} decrease of ≥ 4%) or normoxia during the 6-min walk test.

associations have been suggested between lung volume parameters and D_{LCO} with exercise-induced oxygen desaturation in patients with systemic sclerosis and interstitial lung disease.

Impaired lung volumes, especially TLC, in the desaturation group indicated restrictive abnormalities, confirmed by the higher FEV_1/FVC than in the normoxic group, and the similar PEF to the normoxic group. Moreover, RV/TLC did not differ between the 2 groups, and the mean values were not higher than normal. These results imply no significant obstructive abnormalities in these subjects. Generally, interstitial lung disease shows restrictive abnormalities, including lung volume reduction and the involvement of alveolar-capillary membranes, which reduces the 6MWT distance and lowest S_{pO_2} during 6MWT, due to a disturbance in gas exchange.[15]

The reduced percent-of-predicted D_{LCO} in the desaturation group was most severe, at 45.8% on average, among the lung function parameters. The percent-of-predicted D_{LCO}/V_A was also low, whereas the area under the receiver operating characteristic curve of the percent-of-predicted D_{LCO} was larger than that of D_{LCO}/V_A. It has been suggested that the reduced D_{LCO} was much greater than the loss of lung volume, because of parenchymal abnormalities.[10] Moreover, low D_{LCO} without reduced FVC is the earliest and most sensitive pulmonary functional abnormality in systemic sclerosis.[16] D_{LCO}/V_A is also reduced in many patients, but it usually does not improve the sensitivity for detecting lung disease. The gas transfer reduction is not purely attributable to a loss of lung volume, but might also be secondary to alveolar-capillary membrane thickening and pulmonary vascular disease. In this study, since D_{LCO} was adjusted according to the concentration of hemoglobin, it may be the preferable parameter to reflect alveolar-capillary membrane conductivity and/or pulmonary vasculopathy.[6,17]

The highest percent-of-predicted D_{LCO} value in the desaturation group was 78.0% (results not shown), and the cutoff point for exercise-induced oxygen desaturation was 56.3%. With that criterion, 83% of subjects were correctly predicted regarding oxygen desaturation after 6MWT, and 5 subjects were false negatives. We attempted to detect parameters to identify false negatives to reduce the risk of unexpected exercise-induced oxygen desaturation, and found that lung volume parameters and RVSP were insufficient for that purpose. There might be some other factors that affect oxygen saturation during exercise.

Limitations

We did not evaluate pulmonary arterial hypertension during and after exercise. Patients with interstitial lung disease are prone to pulmonary arterial hypertension at rest and after exercise,[5,18,19] and primary pulmonary hypertension or exercise-induced pulmonary arterial hypertension reduce S_{pO_2}[20] and percent-of-predicted D_{LCO}.[21] Those observations suggest that a high RVSP during exercise may induce oxygen desaturation. RVSP is an estimated value based on pulmonary arterial pressure measured via tissue Doppler echocardiography at rest, without catheterization, and $>$ 40 mm Hg was the criterion for pulmonary arterial hypertension. Although the 5 false negative subjects did not show pulmonary arterial hypertension at rest, there is a possibility that exercise-induced pulmonary arterial hypertension or other pathogenesis may have affected these subjects. Complications associated with systemic sclerosis are multiple,[22] so the number and severity of affected organs differ between individual patients. Further studies of exercise-induced desaturation are required.

Conclusions

Reduced percent-of-predicted lung volumes and of D_{LCO} affected oxygen saturation during 6MWT in patients with systemic sclerosis and interstitial lung disease. Percent-of-predicted D_{LCO} is a good candidate for a sensitive and specific predictor of exercise-induced oxygen desaturation in such patients.

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