

Title; Predictors of exercise-induced oxygen desaturation in systemic sclerosis patients with interstitial lung disease.

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This study has not been previously presented in poster or other sessions.

Conflict of interest;

No potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article for all authors.

### Abstract

**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 this marker in systemic sclerosis patients with interstitial lung disease. We aimed to indicate the predicting factors among pulmonary functions in systemic sclerosis patients for exercise-induced oxygen desaturation.

**Methods:** Data was collected prospectively from 80 of 110 consecutive systemic sclerosis patients with normal oxygen saturation at rest ( $> 95\%$ ) who could perform the six-minute walk test without physical discomfort including leg pain. Parameters from pulmonary function tests and echocardiography were collected for all subjects.

**Results:** Thirty subjects showed a decline ( $\geq 4\%$ ) in oxygen saturation during the six-minute walk test (desaturation group). The other subjects were assigned to the normoxic group. The percent predicted of vital capacity, forced expiratory volume in one second, total lung capacity,  $D_{LCO}$ , and  $D_{LCO}$ /alveolar volume were lower and forced expiratory volume in one second/forced vital capacity was higher in the desaturation group than in the normoxic group. Logistic regression analysis showed the percent predicted of  $D_{LCO}$  as a high accurate parameter for exercise-induced oxygen desaturation and the area under the ROC curve was 0.92 (cut-off point 56.3%, sensitivity 0.83, and specificity 0.86). Five subjects, over the cut-off point of the percent predicted of  $D_{LCO}$  in the desaturation group, could not be distinguished from normoxic subjects using parameters including lung volumes and right ventricular systolic pressure.

**Conclusions:** The factor underlying exercise-induced oxygen desaturation was suggested to be reduced percent predicted of  $D_{LCO}$ , which was useful as a predictor in over 80% of subjects in this population.

Key words: systemic sclerosis; interstitial lung disease; oxygen saturation; pulmonary function; pulmonary arterial hypertension; six-minute walk test.

## Introduction

Exercise-induced oxygen desaturation in patients with interstitial lung disease may be one of the crucial factors in exercise limitation. A fall in SpO<sub>2</sub> to 88% or less during the six-minute walk test (6MWT) indicated high mortality in patients with idiopathic interstitial pneumonia.<sup>1</sup> Oxygen desaturation during 6MWT correlated with the diffusion capacity of the lung for carbon monoxide (D<sub>LCO</sub>).<sup>2,3</sup> Impaired D<sub>LCO</sub> and pulmonary arterial hypertension were also found in patients with systemic sclerosis with respect to pulmonary involvement,<sup>4,5</sup> and low D<sub>LCO</sub> ( $\leq 50\%$ ) was one of the predictors of death.<sup>6</sup> However, oxygen desaturation in SpO<sub>2</sub> ( $\geq 4\%$ ) during 6MWT has been correlated with age, dyspnea index, positive anti-Scl-70 autoantibody, and forced vital capacity (FVC), but D<sub>LCO</sub> was not examined in relation to oxygen saturation in patients with systemic sclerosis.<sup>7</sup>

Identifying the predictive factors of exercise-induced oxygen desaturation would be to select patients who might benefit for additional monitoring using oximetry during 6MWT when oxygen saturation is normal at rest. Moreover, the suggestion of cut-off points for these factors should be also beneficial for alerting patients to avoid hypoxic risk.<sup>8</sup> The present study aimed to prospectively identify the predictive factors of exercise-induced oxygen desaturation in systemic sclerosis patients with interstitial lung

disease using 6MWT as a submaximal exercise.

## Methods

One hundred and ten consecutive adult systemic sclerosis patients with interstitial lung disease were referred to the Division of Rehabilitation Medicine, Kanazawa University Hospital, between 2008 and 2012. Interstitial lung disease was diagnosed by examinations including the pulmonary function test, high resolution CT, and/or open lung biopsy. The main reasons for their visits were for the evaluation and rehabilitation treatment of digit ulcers, joint contracture, and exercise intolerance. The study was approved by the Ethics Committee of the University, and all subjects gave their written informed consent to participate in the study.

Data from 6MWT was obtained if the SpO<sub>2</sub> value was normal (> 95%) at rest in room air. Exclusion criteria for the present study were pain or ulcers in the foot, a severe cough, heart failure, or back pain. Therefore, 80 subjects (66 female and 14 male), with a mean age of 57.4 years, were assigned as subjects to this study (Figure 1). SpO<sub>2</sub> was monitored using a handheld pulse oximeter with a reflectance sensor on the forehead to detect oxygen saturation during 6MWT and was measured at rest and the end of the walk without interfering the test. We avoided using a fingertip sensor for pulse oximetry because digit circulation is often deteriorated in systemic sclerosis patients such that

SpO<sub>2</sub> cannot be measured during 6MWT.<sup>9</sup>

We collected data of the percent predicted of vital capacity (VC), forced expiratory volume in one second (FEV<sub>1</sub>), FEV<sub>1</sub>/FVC, total lung capacity (TLC), peak expiratory flow (PEF), residual volume/TLC (RV/TLC), D<sub>LCO</sub>, and D<sub>LCO</sub>/alveolar volume (D<sub>LCO</sub>/V<sub>A</sub>) from pulmonary function tests using a commercially available system (Chestac-9800, Chest M.I., Tokyo, Japan). Each predicted value was calculated with sex, age, and height,<sup>10</sup> e.g. Baldwin's formula. D<sub>LCO</sub>, by single breath method, was adjusted by hemoglobin concentrations according to Cotes' equation.<sup>2</sup>

Transthoracic echocardiographic imaging was carried out using an iE33 Echocardiography System (Philips, Amsterdam, Netherlands), with subjects 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 (EF) was calculated with modified Simpson's formula. Right ventricular systolic pressure (RVsystP), reflecting systolic pulmonary artery pressure, was estimated from the tricuspid regurgitating velocity following Bernoulli's principle by tissue Doppler echocardiography.<sup>11,12</sup>

## Statistics

The subjects who showed a decline ( $\geq 4\%$ ) in SpO<sub>2</sub> during 6MWT were assigned to the

desaturation group, since a desaturation of 4% or more during exercise has been found to predict mortality<sup>1</sup> and to be an adverse prognostic sign<sup>13</sup> in patients with idiopathic pulmonary fibrosis. The remaining subjects constituted the normoxic group. Differences in the evaluation value between the two groups were compared using the two-tailed *t* test. The chi-square test was used to compare gender distribution and skin involvement subsets (diffuse and limited type). Logistic regression analyses were used for parameters regarding exercise-induced oxygen desaturation. Subsequently, as to parameters with high accuracy in the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity and specificity were obtained from critical points on the ROC curve. Moreover, all subjects were divided by the degree of severity in the percent predicted of  $D_{LCO}$  and evaluation values regarding lung volumes and  $RV_{systP}$  were compared between the two groups using the two-tailed *t* test. Statistical analyses were performed with JMP8.0 (SAS Institute, Cary, NC), except the 95% CI for the AUC using SPSS17.0 (SPSS Inc., Chicago, IL). In all analyses,  $P < 0.05$  was taken to indicate significance.

## Results

The characteristics of subjects in the desaturation group ( $n = 30$ ) and in the normoxic group ( $n = 50$ ) are shown in Table 1. There were no differences in gender distribution, age, skin involvement subsets, the duration of disease after the onset of Raynaud's

phenomenon, RV/TLC (% pred), PEF (% pred), EF, RVsystP, and the 6MWT distance between the desaturation and normoxic groups. The percent predicted of VC, FEV<sub>1</sub>, and TLC, which represented the lung volume, were significantly lower in the desaturation group than in the normoxic group. D<sub>LCO</sub>, D<sub>LCO</sub> (% pred), D<sub>LCO</sub>/V<sub>A</sub>, and D<sub>LCO</sub>/V<sub>A</sub> (% pred) were also significantly lower in the desaturation group. FEV<sub>1</sub>/FVC in the desaturation group was higher than that in the normoxic group.

Logistic regression analyses were used for pulmonary parameters of exercise-induced oxygen desaturation, and the percent predicted of D<sub>LCO</sub> was the highest accurate parameter regarding AUC at 0.92 (Figure 2). At the critical point on the ROC curve, the percent predicted of D<sub>LCO</sub> was 56.3% (sensitivity 0.83 and specificity 0.86). When the cut-off point of the percent predicted of D<sub>LCO</sub> was set to 56.3% for exercise-induced oxygen desaturation, five subjects were in the desaturation group with the percent predicted of D<sub>LCO</sub> > 56.3%, defined as the false negative subjects.

All subjects were classified by the cut-off point of the percent predicted of D<sub>LCO</sub>, and then evaluation values of the percent predicted of VC, FEV<sub>1</sub>, TLC, and RVsystP were compared between the two groups (Figure 3). The percent predicted of VC, FEV<sub>1</sub>, and TLC in the desaturation group over the cut-off point were significantly lower than those in the normoxic group. There was no significant difference in RVsystP between the two

groups. However five false negative subjects showed low values for three lung volume parameters, 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 the classification of the percent predicted of  $D_{LCO}$  severity.

### Discussion

Significantly impaired  $D_{LCO}$  and lung volume parameters, i.e. VC,  $FEV_{1s}$ , and TLC, were found in the desaturation group in this study. 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.<sup>7</sup> The percent predicted of  $D_{LCO}$  has been reported to be one of the predictors of the 6MWT distance in patients with systemic sclerosis with interstitial lung disease.<sup>4</sup> Exercise-induced oxygen desaturation in patients with idiopathic interstitial pneumonia has been correlated with walk-velocity, the percent predicted of  $D_{LCO}$ , and arterial oxygen pressure,<sup>14</sup> the percent predicted of  $D_{LCO}$  and pulmonary capillary blood volume,<sup>3</sup> and  $D_{LCO}$ .<sup>2</sup> In support of these studies, associations have been suggested between lung volume parameters and  $D_{LCO}$  with exercise-induced oxygen desaturation in systemic sclerosis patients with interstitial lung

disease.

Impaired lung volumes, especially TLC, in the desaturation group indicated restrictive abnormalities, which were confirmed by the higher FEV<sub>1</sub>/FVC than, and similar PEF to those in the normoxic group. Moreover, RV/TLC did not differ between the two groups and the mean values were not higher than normal. These results implied no significant obstructive abnormalities in these subjects. Generally, interstitial lung disease shows restrictive abnormalities including lung volume reductions and the involvement of alveolar-capillary membranes, which reduces the 6MWT distance and minimal SpO<sub>2</sub> during 6MWT due to a disturbance in gas exchange.<sup>15</sup>

Reductions in the percent predicted of D<sub>LCO</sub> in the desaturation group were shown to be the most severe at 45.8% on average among the parameters of lung function. The percent predicted of D<sub>LCO</sub>/V<sub>A</sub> was also low, whereas the AUC of the percent predicted of D<sub>LCO</sub> was larger than that of D<sub>LCO</sub>/V<sub>A</sub>. It has been suggested that the reduction in D<sub>LCO</sub> was much greater than the loss of lung volume because of parenchymal abnormalities.<sup>10</sup> Moreover, low D<sub>LCO</sub> without reduction of FVC is the earliest and most sensitive pulmonary functional abnormality in systemic sclerosis.<sup>16</sup> D<sub>LCO</sub>/V<sub>A</sub> is also reduced in many patients, but it usually does not add to sensitivity in 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 to 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.<sup>6,17</sup>

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

This study has a limitation: the lack of evaluations regarding pulmonary arterial hypertension during and after exercise. Patients with interstitial lung disease were prone to pulmonary arterial hypertension at rest and after exercise.<sup>5,18,19</sup> Additionally, primary pulmonary hypertension or exercise-induced pulmonary arterial hypertension has been shown to reduce  $SpO_2$ <sup>20</sup> and the percent predicted of  $D_{LCO}$ .<sup>21</sup> These observations suggested that a high RVsystP during exercise may have induced oxygen desaturation.

RVsystP is an estimated value regarding pulmonary arterial pressure using tissue Doppler echocardiography at rest without catheterization, and 40 mmHg < was the criterion of pulmonary arterial hypertension. Although the five false negative subjects did not show pulmonary arterial hypertension at rest, there was a possibility that exercise-induced pulmonary arterial hypertension or other pathogenesis may have affected these subjects. As complications associated with systemic sclerosis are multiple,<sup>22</sup> the number and severity of affected organs differ between individual patients. Further detailed studies of exercise-induced oxygen desaturation are required.

In conclusion, reductions in the percent predicted of lung volumes and  $D_{LCO}$  affected oxygen saturation during 6MWT in systemic sclerosis subjects with interstitial lung disease. Among the pulmonary factors tested, the percent predicted of  $D_{LCO}$  was found to be a good candidate for a sensitive and specific predictor of exercise-induced oxygen desaturation.

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### Figure legends

#### Figure 1

Flowchart shows study design and number of subjects enrolled in this study.

#### Figure 2

The receiver operating characteristic (ROC) curves of parameters affecting oxygen saturation during six-minute walk test.  $D_{LCO}$ : diffusion capacity of the lung for carbon monoxide; TLC: total lung capacity;  $V_A$ : alveolar volume; VC: vital capacity. The area under the ROC curves (95% CI) were 0.92 (0.85-0.98) in  $D_{LCO}$  (% pred), 0.82 (0.73-0.91) in VC (% pred), 0.84 (0.76-0.93) in TLC (% pred), and 0.70 (0.57-0.82) in  $D_{LCO}/V_A$  (% pred).

#### Figure 3

The distribution of the 80 subjects after they had been classified according to the degree of severity in the diffusion capacity of the lung for carbon monoxide ( $D_{LCO}$ ). D: desaturation group; N: normoxic group. The parameter in (a) is the percent predicted of vital capacity (VC), in (b) is the percent predicted of forced expiratory volume in one second ( $FEV_1$ ), in (c) is the percent predicted total lung capacity (TLC), and in (d) is right ventricular systolic pressure (RVsystP).

Table 1. Characteristics of subjects with systemic sclerosis

Patient characteristics	All patients (n = 80)	Normoxic group (n = 50)	Desaturation group (n = 30)	P (normoxic vs. desaturation group)
Gender (f/m)	66/14	43/7	23/7	0.29
Age (yrs)	57.4 ± 11.8	57.6 ± 12.3	57.0 ± 11.0	0.80
Duration of disease (yrs)	6.6 ± 7.9	6.4 ± 8.5	7.0 ± 7.0	0.73
Subset (diffuse/limited)	45/35	24/26	21/9	0.055
VC (% pred)	94.0 ± 22.9	103.3 ± 21.4	78.5 ± 18.3	< 0.001*
FEV <sub>1</sub> (% pred)	93.9 ± 24.0	101.2 ± 22.4	81.8 ± 21.8	< 0.001*
FEV <sub>1</sub> /FVC	79.9 ± 8.2	78.3 ± 8.5	82.5 ± 7.0	0.021*
PEF (% pred)	87.5 ± 16.5	88.2 ± 18.4	86.3 ± 15.6	0.61
TLC (% pred)	85.9 ± 20.4	95.1 ± 16.3	70.5 ± 17.1	< 0.001*
RV/TLC (%)	95.5 ± 15.7	97.1 ± 14.7	92.9 ± 17.3	0.28
D <sub>LCO</sub> (mL/min/mmHg)	13.8 ± 4.5	16.0 ± 3.7	10.3 ± 3.2	< 0.001*
D <sub>LCO</sub> (% pred)	62.6 ± 19.5	72.7 ± 15.7	45.8 ± 12.4	< 0.001*
D <sub>LCO</sub> /V <sub>A</sub> (mL/min/mmHg/L)	4.44 ± 1.13	4.68 ± 0.98	4.06 ± 1.28	0.027*
D <sub>LCO</sub> /V <sub>A</sub> (% pred)	84.9 ± 19.9	89.9 ± 17.6	76.2 ± 21.1	0.0048*
EF (%)	72.1 ± 4.7	72.4 ± 5.2	71.6 ± 3.9	0.43
RVsystP (mmHg)	31.1 ± 9.8	29.8 ± 8.2	33.2 ± 11.9	0.18
6MWT distance (m)	492 ± 102	504 ± 93	472 ± 115	0.21

Values are means ± SD. \* $P < 0.05$ . 6MWT: six-minute walk test; D<sub>LCO</sub>: diffusion capacity of the lung for carbon monoxide; EF: left ventricular ejection fraction; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; RV: residual volume; RVsystP: right ventricular systolic pressure; TLC: total lung capacity; V<sub>A</sub>: alveolar volume; VC: vital capacity.

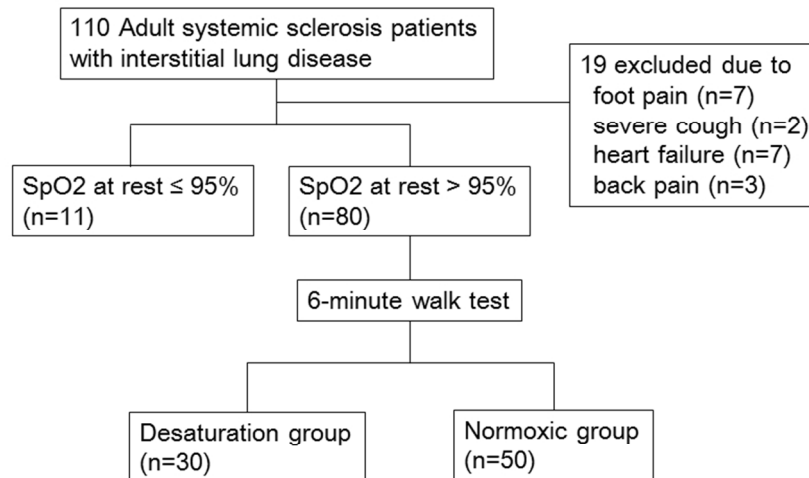


Figure 1. Flowchart shows study design and number of subjects enrolled in this study.  
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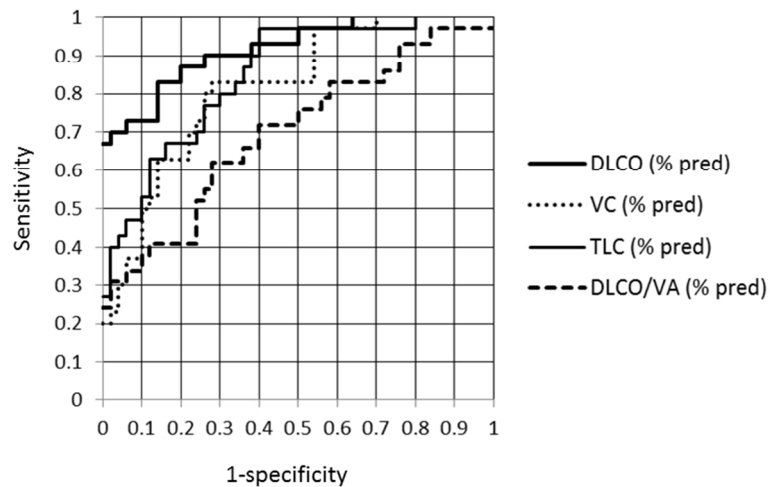


Figure 2. The receiver operating characteristic (ROC) curves of parameters affecting oxygen saturation during six-minute walk test. DLCO: diffusion capacity of the lung for carbon monoxide; TLC: total lung capacity; VA: alveolar volume; VC: vital capacity. The area under the ROC curves (95% CI) were 0.92 (0.85-0.98) in DLCO (% pred), 0.82 (0.73-0.91) in VC (% pred), 0.84 (0.76-0.93) in TLC (% pred), and 0.70 (0.57-0.82) in DLCO/VA (% pred).  
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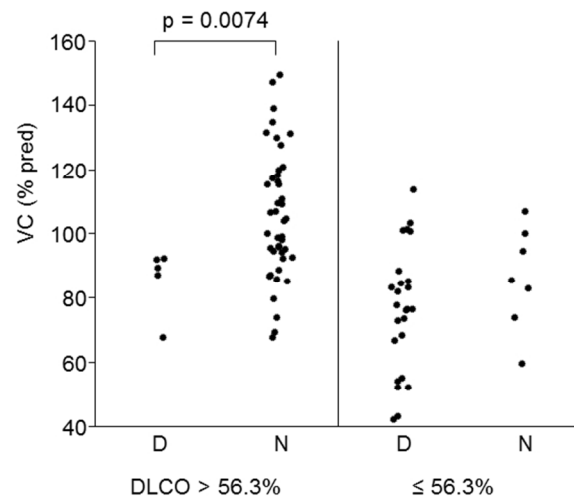
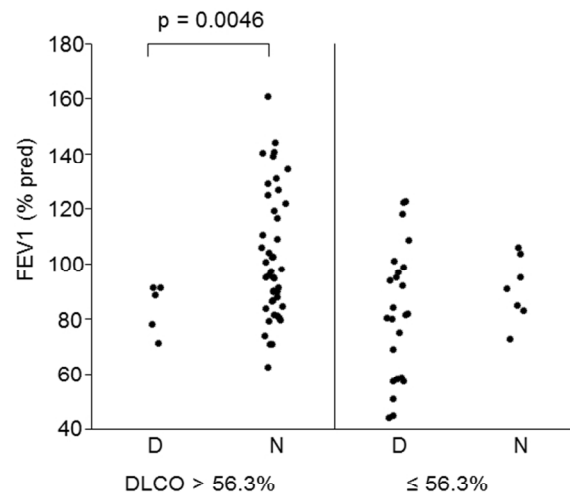
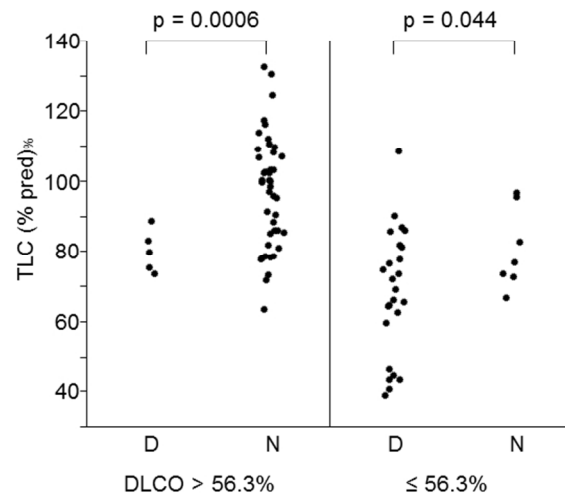


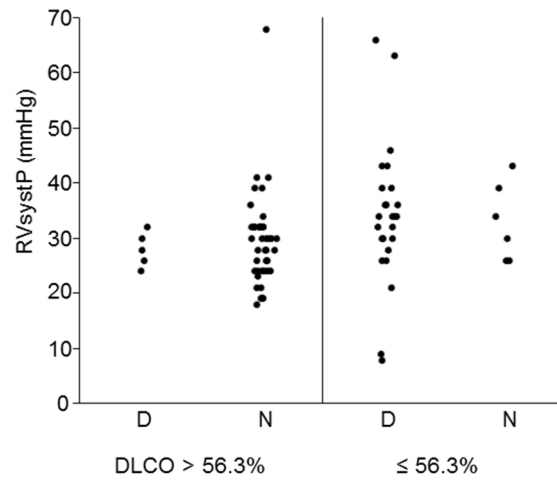
Figure 3. The distribution of the 80 subjects after they had been classified according to the degree of severity in the diffusion capacity of the lung for carbon monoxide (DLCO). D: desaturation group; N: normoxic group. The parameter in (a) is the percent predicted of vital capacity (VC), in (b) is the percent predicted of forced expiratory volume in one second (FEV1), in (c) is the percent predicted total lung capacity (TLC), and in (d) is right ventricular systolic pressure (RVsystP).  
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