Exertional Desaturation as a Predictor of Rapid Lung Function Decline in COPD

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Key Words
Chronic obstructive pulmonary disease · Computed tomography · Emphysema · Exertional desaturation · Lung function

Abstract
Background: To date, no clinical parameter has been associated with the decline in lung function other than emphysema severity in COPD. Objectives: The main purpose of this study was to explore whether the rate of lung function decline differs between COPD patients with and without exertional desaturation. Methods: A total of 224 subjects were selected from the Korean Obstructive Lung Disease cohort. Exertional desaturation was assessed using the 6-min walk test (6MWT), and defined as a post-exercise oxygen saturation ($SpO_2$) of <90% or a ≥4% decrease. The cohort was divided into desaturator (n = 47) and non-desaturator (n = 177) groups. Results: There was a significant difference between
the desaturator and non-desaturator groups in terms of the change in pre-bronchodilator forced expiratory volume in 1 s (FEV₁) over a 3-year period of follow-up (p = 0.006). The mean rate of decline in FEV₁ was greater in the desaturator group (33.8 ml/year) than in the non-desaturator group (11.6 ml/year). A statistically significant difference was also observed between the two groups in terms of the change in the St. George’s Respiratory Questionnaire (SGRQ) total score over 3 years (p = 0.001). **Conclusions:** This study suggests, for the first time, that exertional desaturation may be a predictor of rapid decline in lung function in patients with COPD. The 6MWT may be a useful test to predict a rapid lung function decline in COPD.

**Introduction**

Chronic obstructive pulmonary disease (COPD) is a major cause of death in most countries and will become the third leading cause of death worldwide by 2020 [1]. COPD is defined as the presence of airflow limitation that is not fully reversible. Treatment is mostly determined by the severity of this airflow limitation. However, COPD shows considerable heterogeneity in terms of clinical presentation and disease progression [2]. Therefore, COPD is now considered to be a spectrum of smoking-related lung diseases rather than a single disease entity [3]. These variable manifestations may represent distinct COPD phenotypes, and numerous trials have attempted to describe the physiological, epidemiological, and clinical significance of each subtype [2, 3].

The risk of alveolar hypoxia and consequent hypoxemia increases as COPD progresses. Hypoxemia contributes to reduced health-related quality of life, diminished exercise tolerance, reduced skeletal muscle function, and ultimately an increased risk of death in patients with COPD [4]. However, the prevalence of hypoxemia among COPD patients remains uncertain. Severe hypoxemia is relatively uncommon, and long-term administration of oxygen has been shown to increase survival in such patients [5]. Although reports on the prevalence of exertional desaturation without resting hypoxemia in COPD are rare [6, 7], some research suggests that exertional desaturation may be a predictor of mortality in these patients with COPD [8–10].

The rate of lung function decline is one of the most important outcome measures in COPD. Many studies have demonstrated that the rate of lung function decline is closely tied to smoking status: greatest in current smokers, less in former smokers, and even less in never-smokers [11]. Recently, Nishimura et al. [12] reported the results of a multicenter observational study examining the serial change in lung function in a cohort of 279 patients with COPD, in which emphysema severity was independently associated with a rapid annual decline [12]. The association between the baseline radiologic burden of emphysema and the subsequent decline in lung function is consistent with other recent data published by both Vestbo et al. [13] and Mohamed Hoesin et al. [14]. Until now, no clinical parameter has been suggested as a predictor of rapid lung function decline other than current smoking and emphysema severity in COPD.

The main purpose of this study was to explore whether the rate of lung function decline differs between COPD patients with and without exertional desaturation. We also tried to demonstrate the correlation of exertional desaturation with CT emphysema severity to support this hypothesis.

**Materials and Methods**

**Subjects**

The Korean Obstructive Lung Disease (KOLD) cohort comprises patients with COPD or asthma recruited from the pulmonary clinics of 11 referring hospitals in South Korea between June 2005 and October 2010. The inclusion criteria for the present study were: a post-bronchodilator forced expiratory volume in 1 s (FEV₁)-to-forced vital capacity (FVC) ratio <0.7; a smoking history ≥10 pack-years; an oxygen saturation (SpO₂) on room air ≥90% according to pulse oximetry, and the availability of volumetric CT data. Among 301 patients with COPD in the KOLD cohort, 77 patients did not satisfy the inclusion criteria (12 patients had no SpO₂ data, 1 patient had an SpO₂ <90%, and 64 patients had no analyzed volumetric CT data). Finally, a total of 224 subjects were selected from the KOLD cohort.

The study was approved by the institutional review boards of all 11 participating hospitals. Written informed consent was obtained from all patients.

**Treatment Protocol**

Baseline clinical data were obtained after cessation of the following respiratory medications: inhaled corticosteroids for 2 weeks, inhaled long-acting β-agonists for 2 days, and inhaled short-acting β-agonists or inhaled short-acting anti-cholinergics for 12 h. The patients were then treated for 3 months with a combination of inhaled corticosteroids and long-acting β-agonists. Thereafter, individualized treatment was allowed. Lung function and health-related quality of life were then measured repeatedly over a period of 3 years.

**Lung Function Measurements**

Spirometry was performed using Vmax 22 (Sensor Medics, Yorba Linda, Calif., USA) and PFDX (Medgraphics, St. Paul, Minn., USA), as recommended by the American Thoracic Society.
Exertional Desaturation and Lung Function Decline in COPD

The following values were obtained: FEV₁, FVC, and the FEV₁/FVC ratio. Post-bronchodilator spirometry values were obtained 15 min after the administration of a 400-μg dose of salbutamol. This was delivered via a metered dose inhaler connected to a spacer. Lung volumes, including residual volume (RV), vital capacity (VC), and total lung capacity (TLC), were measured using body plethysmography (V6200, SensorMedics, or PFDX) [16]. Diffusing capacity was measured by assessing the single-breath carbon monoxide uptake (Vmax 22 or PFDX) [17].

**Exercise Test and Definition of Exertional Desaturation**

Exercise capacity and exertional desaturation were assessed using the 6-min walk test (6MWT). The particular form of exercise taken may affect the ability to detect exertional desaturation in patients with COPD, and the 6MWT has been shown to be more sensitive than maximal incremental cycle testing for detecting oxygen desaturation [18]. Exertional desaturation was defined as a post-exercise SpO₂ <90% or a ≥4% decrease compared to baseline.

**CT Measurement of Airway and Lung Parenchyma**

Prior to inclusion in the present study, all patients had undergone volumetric CT scans during full inspiration and expiration using a 16-multidetector CT scanner (Somatom Sensation; Siemens, Erlangen, Germany; GE Lightspeed Ultra Instrument, General Electric Healthcare, Milwaukee, Wisc., USA; Philips Brilliance Instrument, Philips Medical Systems, Best, The Netherlands). Images of the whole lung were extracted automatically and the attenuation coefficient of each pixel was calculated. The cut-off level between normal lung density and low-attenuation areas was defined as −950 Hounsfield units (HU) [19].

The volume fraction of the lung below −950 HU was calculated automatically at full inspiration and termed the emphysema index. The mean lung density was calculated automatically during expiration and inspiration. The air-trapping index was estimated by calculating the ratio of the mean lung density at expiration and inspiration [20]. Airway dimensions were measured near the origin of the two segmental bronchi (RB1, LB1 + 2). Airway dimensions [wall area (WA), lumen area (LA) and wall area percentage (WA%)] were measured in each bronchus. WA% was defined as WA/(WA + LA) × 100 and termed the airway index [20].

**St. George’s Respiratory Questionnaire**

The validated Korean version of the St. George’s Respiratory Questionnaire (SGRQ) was used to assess health-related quality of life [21]. The SGRQ covers 3 domains: symptoms (relating to cough, sputum, wheeze, and shortness of breath), activity (relating to physical activities that cause or are limited by breathlessness), and impact (relating to control, panic, medication, and expectations). The total score ranges from 0 to 100, with a lower score representing better health-related quality of life. A change of 4 units indicates a clinically relevant change.

**Statistical Analysis**

All statistical analyses were performed using the statistical software package SPSS v12.0.1 (SPSS Inc., Chicago, Ill., USA). Bivariate comparisons were made using Pearson’s χ² test, Student’s t test, and the Mann-Whitney U test. Logistic regression analysis was used to identify independent predictors of exertional desaturation. To assess changes over time in FEV₁ and SGRQ score, repeated measures analysis of variance (ANOVA) was performed. The last observation carried forward method was used for missing data. p ≤ 0.05 was considered statistically significant.

**Results**

**Baseline Characteristics**

The mean age of the 224 patients was 66 years. The sample included only 8 (3.6%) females. The mean body mass index (BMI) was 22.9. The average smoking history, measured in terms of pack-years, was 46.2 years. A total of 77 (34.4%) patients were current smokers. During baseline spirometry, the mean post-bronchodilator FEV₁ was 1.62 liters/min (53.0% of predicted value) and most patients had moderate-to-severe COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Of these, 4.5% were classified as GOLD I (mild COPD), 51.8% as GOLD II (moderate COPD), 36.6% as GOLD III (severe COPD), and 7.1% as GOLD IV (very severe COPD).

**Prevalence of Exertional Desaturation and Differences between Study Groups**

Exertional desaturation was detected in 47 patients (21%) after the 6MWT. The baseline data of the desaturator group (n = 47) and the non-desaturator group (n = 177) were then compared. Statistically significant differences between the groups were observed for age, BMI, dyspnea scale, BODE index, FEV₁, diffusing capacity, and resting SpO₂. The CT emphysema index and the air-trapping index were significantly higher in the desaturator group (p = 0.000 and p = 0.024, respectively). The mean SGRQ total score was higher in the desaturator group, although this did not reach statistical significance (p = 0.053). No differences between the groups were observed for smoking status, comorbidity index, RV, TLC, 6-min walk distance, or the airway index (table 1).

**Changes in Lung Function and Health-Related Quality of Life at the 3-Year Follow-Up**

Data from a total of 189 subjects recruited prior to October 2008 were available for the 3-year follow-up analyses performed in November 2011. Repeated measures ANOVA revealed statistically significant differences between the desaturator and non-desaturator groups in terms of the change in pre-bronchodilator FEV₁ over 3 years (p = 0.006). The mean rate of decline in FEV₁ was greater in the desaturator group (33.8 ml/year) than in the non-desaturator group (11.6 ml/
year). A statistically significant difference was also observed between the two groups in terms of the change in SGRQ total score over 3 years \((p = 0.001)\). Health-related quality of life showed a more rapid worsening in the desaturator group (fig. 1).

Factors Associated with Exertional Desaturation
Multivariate logistic regression analysis was performed to demonstrate independent factors associated with exertional desaturation in patients with COPD. The CT emphysema index was independently associated with exertional desaturation, and the relative risk (RR) was 1.029 (95% CI 1.002–1.057; \(p = 0.037)\). However, no statistically significant association was found for age, \(\text{FEV}_1\), the BODE index, or the air-trapping index (table 2).

Exacerbation during the First Year of Follow-Up
Exacerbation was defined as an increase in the severity of at least one respiratory symptom (dyspnea, sputum, or sputum purulence) for a period of 2 days or more that required additional treatment or unscheduled hospital visits.

No significant differences between the groups were observed in terms of the number of patients with an exacerbation or the number of patients requiring hospitalization due to exacerbation for the first year of follow-up. The mean number of exacerbations or the mean number of hospitalizations due to exacerbation also did not differ significantly between the two groups. The mean number of exacerbations per patient during the first year of follow-up was 1.1 (table 3).

Discussion
The primary aim of this study was to explore whether the rate of lung function decline differs between COPD patients with and without exertional desaturation. Research has already suggested that COPD patients with exertional desaturation are more likely to show a poor prognosis in terms of mortality [8–10]. However, no previous reports have evaluated the change in pulmonary function or health-related quality of life in COPD patients with exertional desaturation over time. Three-year follow-up

Table 1. Baseline characteristics of the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Desaturator group ((n = 47))</th>
<th>Non-desaturator group ((n = 177))</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68.7 ± 6.3</td>
<td>65.4 ± 7.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Male/female</td>
<td>44/3</td>
<td>172/5</td>
<td>0.369</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>36 (76.6)</td>
<td>111 (62.7)</td>
<td>0.075</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>45.0 ± 23.8</td>
<td>46.5 ± 25.3</td>
<td>0.704</td>
</tr>
<tr>
<td>Comorbidity (Charlson index)</td>
<td>1.53 ± 0.62</td>
<td>1.65 ± 0.68</td>
<td>0.281</td>
</tr>
<tr>
<td>BMI</td>
<td>21.4 ± 3.4</td>
<td>23.4 ± 3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline spirometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{FEV}_1), l</td>
<td>1.38 ± 0.52</td>
<td>1.68 ± 0.55</td>
<td>0.001</td>
</tr>
<tr>
<td>(\text{FEV}_1), % of predicted value</td>
<td>47.2 ± 15.8</td>
<td>54.5 ± 15.5</td>
<td>0.005</td>
</tr>
<tr>
<td>(\text{FVC}), l</td>
<td>3.29 ± 0.82</td>
<td>3.44 ± 0.78</td>
<td>0.251</td>
</tr>
<tr>
<td>(\text{FVC}), % of predicted value</td>
<td>81.4 ± 18.3</td>
<td>81.2 ± 15.6</td>
<td>0.929</td>
</tr>
<tr>
<td>(\text{TLC}), l</td>
<td>108.5 ± 17.0</td>
<td>106.3 ± 16.3</td>
<td>0.419</td>
</tr>
<tr>
<td>(\text{RV}), l</td>
<td>3.33 ± 1.15</td>
<td>3.18 ± 1.19</td>
<td>0.433</td>
</tr>
<tr>
<td>(\text{RV}), % of predicted value</td>
<td>137.3 ± 42.9</td>
<td>134.6 ± 50.3</td>
<td>0.735</td>
</tr>
<tr>
<td>(\text{DLCO}), ml/mm Hg/min</td>
<td>11.04 ± 4.68</td>
<td>15.96 ± 5.98</td>
<td>0.000</td>
</tr>
<tr>
<td>(\text{DLCO}), % of predicted value</td>
<td>56.0 ± 22.0</td>
<td>76.7 ± 25.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Dyspnea scale (MMRC scale)</td>
<td>1.98 ± 1.15</td>
<td>1.55 ± 0.94</td>
<td>0.008</td>
</tr>
<tr>
<td>Six-minute walk distance, m</td>
<td>416.3 ± 105.7</td>
<td>445.7 ± 78.2</td>
<td>0.080</td>
</tr>
<tr>
<td>BODE index</td>
<td>2.3 ± 96.6</td>
<td>2.6 ± 94.2</td>
<td>0.024</td>
</tr>
<tr>
<td>SGRQ total score, units</td>
<td>39.7 ± 17.2</td>
<td>34.1 ± 17.7</td>
<td>0.053</td>
</tr>
<tr>
<td>CT measurements†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema index†</td>
<td>32.3 ± 16.3</td>
<td>22.1 ± 14.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Air-trapping index†</td>
<td>95.5 ± 2.6</td>
<td>94.2 ± 3.7</td>
<td>0.024</td>
</tr>
<tr>
<td>Airway index</td>
<td>67.3 ± 4.6</td>
<td>66.4 ± 5.1</td>
<td>0.288</td>
</tr>
<tr>
<td>Resting (\text{SpO}_2), %</td>
<td>95.7 ± 2.3</td>
<td>96.6 ± 1.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. DLCO = Carbon monoxide diffusing capacity; MMRC = Modified Medical Research Council.

† Scores on the SGRQ range from 0 to 100, with lower scores indicating improvement; a change of 4 units or more is considered clinically meaningful.

‡ The volume fraction of the lung below –950 HU was calculated automatically at full inspiration and termed the emphysema index. The air-trapping index was estimated by calculating the ratio of mean lung density at expiration and inspiration. The airway index was defined as the ratio of wall area per wall area plus lumen area.

Table 2. Factors associated with exertional desaturation

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema index†</td>
<td>1.029</td>
<td>1.002–1.057</td>
<td>0.037</td>
</tr>
<tr>
<td>Age</td>
<td>1.051</td>
<td>0.999–1.105</td>
<td>0.053</td>
</tr>
<tr>
<td>BODE index</td>
<td>1.192</td>
<td>1.095–1.571</td>
<td>0.211</td>
</tr>
<tr>
<td>Air-trapping index†</td>
<td>0.997</td>
<td>0.873–1.137</td>
<td>0.959</td>
</tr>
<tr>
<td>(\text{FEV}_1), % of predicted value</td>
<td>1.001</td>
<td>0.966–1.036</td>
<td>0.970</td>
</tr>
</tbody>
</table>

† The volume fraction of the lung below –950 HU was calculated automatically at full inspiration and termed the emphysema index. The air-trapping index was estimated by calculating the ratio of mean lung density at expiration and inspiration.
data for FEV$_1$ and the SGRQ score were available for 189
subjects from the present cohort. Analysis showed that
the rate of decline in FEV$_1$ was more rapid and health-
related quality of life worsened faster in the desaturator
group. It is noteworthy that the present study suggests
exertional desaturation as a new clinical parameter,
which may predict rapid lung function decline in patients
with COPD. Exertional desaturation can be easily as-
essed using the 6MWT without any harm, but CT scan
has high costs and problems related with exposure to ra-
diation. The 6MWT may be a more useful test to identify
decliners among patients with COPD.

According to the clinical trials of pharmacotherapy
for COPD, none of the existing medications for COPD
has been shown to modify the long-term decline in lung
function. Actually, COPD is characterized by progres-
sive airflow limitation but shows considerable heteroge-
neity in clinical presentation and disease progression.
Thus, investigation of clinical factors associated with
rapid lung function decline is important in assessing and
treating patients with COPD. Until now, emphysema se-
verity measured by CT has been the only clinical param-
eter validated as a predictor of rapid lung function de-
cline in COPD [12–14]. The most recent report from the

Fig. 1. Changes in lung function (a) and
health-related quality of life (b).
Hokkaido COPD Cohort study found that emphysema severity was independently associated with a rapid annual decline in FEV\textsubscript{1} in COPD [12]. Another recent report from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study also found that the rate of change in FEV\textsubscript{1} among patients with COPD was highly variable, and that more rapid rates of decline were observed in patients with emphysema [13].

The CT emphysema index was independently associated with exertional desaturation in the present cohort. Only two previous studies investigated the correlation of CT emphysema severity and exertional desaturation. Biernacki et al. [22] suggested that the extent of emphysema, as measured by the CT density histogram, did not correlate with the fall in the partial pressure of oxygen in arterial blood during exercise. However, Taguchi et al. [23] showed that the CT score of emphysema severity was significantly correlated with both the minimal SpO\textsubscript{2} and the change in SpO\textsubscript{2} during exercise. The authors defined emphysema severity according to the density and distribution of low-attenuation areas [23]. These conflicting results probably result from the use of differing methods to measure the severity of emphysema on CT images. In recent years, CT technology and image analysis have advanced considerably, and more accurate detection of lung parenchyma destruction and measurement of emphysema extent are now possible. The density mask technique is widely accepted for the quantification of emphysema, and the threshold for measuring emphysematous pixels varies from \(<-900\) HU to \(<-960\) HU [24]. We used \(-950\) HU as the threshold for detecting emphysema, since previous studies have shown that this criterion correlated well with macroscopic and microscopic measurements [19, 25]. The positive correlation of the CT emphysema index and exertional desaturation supports the main result of the present study that the rate of lung function decline was more rapid in the desaturator group, because CT emphysema severity was a validated predictor of rapid lung function decline in patients with COPD.

Several studies have found that diffusing capacity is significantly correlated with exertional desaturation in COPD patients [26–29]. Other studies have reported a negative correlation between diffusing capacity and the severity of emphysema in patients with COPD [24, 30, 31]. The correlation coefficient for the CT emphysema index and diffusing capacity for carbon monoxide (% of predicted value) obtained in the present study is similar to those reported previously (\(r = -0.65, p = 0.01\)) [24, 30, 31]. Thus, diffusing capacity was not included in the present logistic regression analysis.

The present study had several limitations. First, exertional desaturation was assessed using post-exercise SpO\textsubscript{2} rather than nadir SpO\textsubscript{2}. The KOLD cohort was not originally intended for use in the evaluation of risk factors for exertional desaturation, and so nadir SpO\textsubscript{2} data were unavailable from several of the participating hospitals. The availability of nadir SpO\textsubscript{2} may have led to the identification of more patients with exertional desaturation. Previous reports concerning the time to desaturation during the 6MWT found that early desaturators had a higher probability of desaturation while performing daily activities and of developing severe hypoxemia requiring long-term oxygen therapy [32, 33]. Thus more detailed analyses of the clinical course of COPD patients with exertional desaturation might be possible using nadir SpO\textsubscript{2} and time to desaturation during the 6MWT. Second, a relatively small number of female patients were included. Therefore, the results cannot be generalized to female COPD patients, since a previous study suggests that gender might influence COPD manifestations [34].

In conclusion, the rate of decline in FEV\textsubscript{1} and the change in health-related quality of life were greater in COPD patients with exertional desaturation compared to those without over a 3-year period of follow-up. This suggests that exertional desaturation is a predictor of rapid decline in lung function in patients with COPD. The 6MWT may be a valuable test to identify rapid decliners and to predict the prognosis of patients with COPD. Further studies in large patient samples are warranted to clarify the results of the present study and the feasibility of the 6MWT in estimating rapid decline in lung function in COPD.
Acknowledgements

This study was supported by a grant from the Korea Health-care Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065).

Financial Disclosure and Conflicts of Interest


J.B. Seo was an investigator in a government-sponsored study (2006–2008 Korea Science and Engineering Foundation).

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