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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

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the desaturator and non-desaturator groups in terms of the change in pre-bronchodilator forced expiratory volume in 1 s (FEV_1) over a 3-year period of follow-up ($p = 0.006$). The mean rate of decline in FEV_1 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 Hoesein 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 (FEV_1)-to-forced vital capacity (FVC) ratio <0.7; a smoking history ≥10 pack-years; an oxygen saturation (SpO_2) 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 SpO_2 data, 1 patient had an SpO_2 <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

[15]. The following values were obtained: FEV_1, FVC, and the FEV_1/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 SpO_2 <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 percent (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 χ^2 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 FEV_1 and SGRQ score, repeated measures analysis of variance (ANOVA) was performed. The last observation carried forward method was used for missing data. $p \leq 0.05$ 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 FEV_1 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, FEV_1, diffusing capacity, and resting SpO_2. 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 FEV_1 over 3 years (p = 0.006). The mean rate of decline in FEV_1 was greater in the desaturator group (33.8 ml/year) than in the non-desaturator group (11.6 ml/

Table 1. Baseline characteristics of the two study groups

	Desaturator group (n = 47)	Non-desaturator group (n = 177)	p value
Age, years	68.7 ± 6.3	65.4 ± 7.7	0.007
Male/female ratio	44/3	172/5	0.369
Smoking status			
Current smokers, n (%)	36 (76.6)	111 (62.7)	0.075
Smoking history, pack-years	45.0 ± 23.8	46.5 ± 25.3	0.704
Comorbidity (Charlson index)	1.53 ± 0.62	1.65 ± 0.68	0.281
BMI	21.4 ± 3.4	23.4 ± 3.3	0.001
Baseline spirometry			
FEV_1, l	1.38 ± 0.52	1.68 ± 0.55	0.001
FEV_1, % of predicted value	47.2 ± 15.8	54.5 ± 15.5	0.005
FVC, l	3.29 ± 0.82	3.44 ± 0.78	0.251
FVC, % of predicted value	81.4 ± 18.3	81.2 ± 15.6	0.929
TLC, l	6.54 ± 1.14	6.51 ± 1.16	0.866
TLC, % of predicted value	108.5 ± 17.0	106.3 ± 16.3	0.419
RV, l	3.33 ± 1.15	3.18 ± 1.19	0.433
RV, % of predicted value	137.3 ± 42.9	134.6 ± 50.3	0.735
DLCO, ml/mm Hg/min	11.04 ± 4.68	15.96 ± 5.98	0.000
DLCO, % of predicted value	56.0 ± 22.0	76.7 ± 25.7	0.000
Dyspnea scale (MMRC scale)	1.98 ± 1.15	1.55 ± 0.94	0.008
Six-minute walk distance, m	416.3 ± 105.7	445.7 ± 78.2	0.080
BODE index	3.53 ± 2.17	2.25 ± 1.77	0.000
SGRQ total score†, units	39.7 ± 17.2	34.1 ± 17.7	0.053
CT measurements‡			
Emphysema index (%)	32.3 ± 16.3	22.1 ± 14.9	0.000
Air-trapping index (%)	95.5 ± 2.6	94.2 ± 3.7	0.024
Airway index (%)	67.3 ± 4.6	66.4 ± 5.1	0.288
Resting SpO_2, %	95.7 ± 2.3	96.6 ± 1.5	0.001

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.

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, FEV_1, the BODE index, or the air-trapping index (table 2).

Table 2. Factors associated with exertional desaturation

	RR	95% CI	p value
Emphysema index†	1.029	1.002–1.057	0.037
Age	1.051	0.999–1.105	0.053
BODE index	1.192	0.905–1.571	0.211
Air-trapping index†	0.997	0.873–1.137	0.959
FEV_1 (% of predicted value)	1.001	0.966–1.036	0.970

† 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.

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

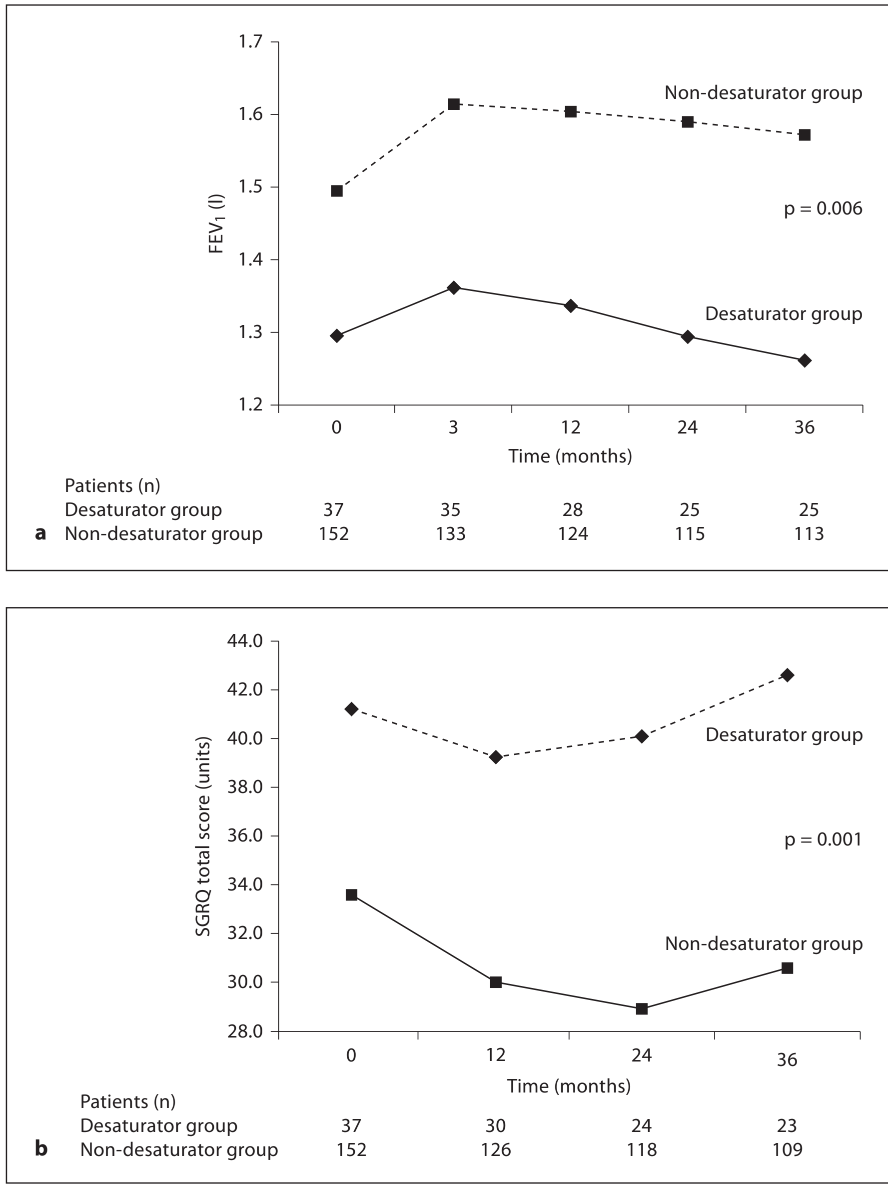

Fig. 1. Changes in lung function (**a**) and health-related quality of life (**b**).

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 assessed using the 6MWT without any harm, but CT scan has high costs and problems related with exposure to radiation. 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 progressive airflow limitation but shows considerable heterogeneity 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 severity measured by CT has been the only clinical parameter validated as a predictor of rapid lung function decline in COPD [12–14]. The most recent report from the

Table 3. Exacerbation during the first year of follow-up

	Desaturator group (n = 36)	Non-desaturator group (n = 146)	p value
Patients with exacerbation, n (%)			
Total	16 (44.4)	65 (44.5)	0.993
Leading to hospitalization	3 (8.3)	14 (9.6)	0.817
Exacerbations, n			
Mean number	1.00 ± 1.45	1.11 ± 1.67	0.899
Leading to hospitalization	0.08 ± 0.28	0.12 ± 0.38	0.883

Values for exacerbations are presented as means ± SD. The Mann-Whitney U test was used for comparing numbers of subjects with exacerbation and admissions.

Hokkaido COPD Cohort study found that emphysema severity was independently associated with a rapid annual decline in FEV_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_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_2 and the change in SpO_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_2 rather than nadir SpO_2. The KOLD cohort was not originally intended for use in the evaluation of risk factors for exertional desaturation, and so nadir SpO_2 data were unavailable from several of the participating hospitals. The availability of nadir SpO_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_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_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.

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Financial Disclosure and Conflicts of Interest

C. Kim, S.M. Lee, J.S. Lee, J.W. Huh, J.H. Lee, S.W. Ra, J.-H. Lee, E.-K. Kim, T.-H. Kim, W.J. Kim, S.-M. Lee, S.Y. Lee, S.Y. Lim, T.R. Shin, H.I. Yoon, S.S. Sheen, and Y.B. Park have no conflicts of interest to disclose.

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

Y.-M. Oh has been an investigator in industry-sponsored studies (MSD Korea, AstraZeneca Korea, Boehringer Ingelheim Korea, Handok, and GlaxoSmithKline) and in university-sponsored studies (Asan Institute for Life Science, University of Ulsan College of Medicine). Y.M. Oh has participated as a speaker at scientific meetings organized and financed by pharmaceutical companies (Handok, Pfizer Korea, GlaxoSmithKline, AstraZeneca Korea, MSD Korea, and Boehringer Ingelheim Korea) and a magazine company (Korea Doctors' Weekly). Y.M. Oh developed an educational presentation for a pharmaceutical company (Diachi Sankyo Korea).

S.-D. Lee serves as a consultant to GlaxoSmithKline and Nycomed and has participated as a speaker at scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, Nycomed, and Boehringer Ingelheim).

References

1 GOLD – Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop Report (NIH publication No 2701:1–100). Bethesda, National Heart, Lung and Blood Institute. 2001. http://www.goldcopd.com (accessed December 2010).

2 Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, Fabbri LM, Goldin JG, Jones PW, Macnee W, Make BJ, Rabe KF, Rennard SI, Sciurba FC, Silverman EK, Vestbo J, Washko GR, Wouters EF, Martinez FJ: Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182:598–604.

3 Friedlander AL, Lynch D, Dyar LA, Bowler RP: Phenotypes of chronic obstructive pulmonary disease. COPD 2007;4:355–384.

4 Kim V, Benditt JO, Wise RA, Sharafkhaneh A: Oxygen therapy in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008;5:513–518.

5 Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial – Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93:391–398.

6 Panos RJ, Eschenbacher W: Exertional desaturation in patients with chronic obstructive pulmonary disease. COPD 2009;6:478–487.

7 van Gestel AJR, Clarenbach CF, Stöwhas AC, Teschler S, Russi EW, Teschler H, Kohler M: Prevalence and prediction of exercise-induced oxygen desaturation in patients with chronic obstructive pulmonary disease. Respiration 2012;84:353–359.

8 Tojo N, Ichioka M, Chida M, Miyazato I, Yoshizawa Y, Miyasaka N: Pulmonary exercise testing predicts prognosis in patients with chronic obstructive pulmonary disease. Intern Med 2005;44:20–25.

9 Takigawa N, Tada A, Soda R, Date H, Yamashita M, Endo S, Takahashi S, Kawata N, Shibayama T, Hamada N, Sakaguchi M, Hirano A, Kimura G, Okada C, Takahashi K: Distance and oxygen desaturation in 6-min walk test predict prognosis in copd patients. Respir Med 2007;101:561–567.

10 Casanova C, Cote C, Marin JM, Pinto-Plata V, de Torres JP, Aguirre-Jaime A, Vassaux C, Celli BR: Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. Chest 2008;134:746–752.

11 Lee PN, Fry JS: Systematic review of the evidence relating FEV_1 decline to giving up smoking. BMC Med 2010;8:84.

12 Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, Shimizu K, Betsuyaku T, Ito YM, Fuke S, Igarashi T, Akiyama Y, Ogura S: Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;185:44–52.

13 Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Coxson HO, Crim C, Lomas DA, MacNee W, Miller BE, Silverman EK, Tal-Singer R, Wouters E, Rennard SI: Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011;365:1184–1192.

14 Mohamed Hoesein FA, de Hoop B, Zanen P, Gietema H, Kruitwagen CL, van Ginneken B, Isgum I, Mol C, van Klaveren RJ, Dijkstra AE, Groen HJ, Boezen HM, Postma DS, Prokop M, Lammers JW: CT-quantified emphysema in male heavy smokers: association with lung function decline. Thorax 2011;66:782–787.

15 Standardization of spirometry, 1994 update: American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107–1136.

16 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows: report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal – official statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

17 American Thoracic Society: Single-breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique – 1995 update. Am J Respir Crit Care Med 1995;152:2185–2198.

18 Poulain M, Durand F, Palomba B, Ceugniet F, Desplan J, Varray A, Prefaut C: 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. Chest 2003;123:1401–1407.

19 Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC: Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1995;152:653–657.

20 Lee YK, Oh YM, Lee JH, Kim EK, Lee JH, Kim N, Seo JB, Lee SD: Quantitative assessment of emphysema, air trapping, and airway thickening on computed tomography. Lung 2008;186:157–165.

21 Kim YS, Byun MK, Jung WY, Jeong JH, Choi SB, Kang SM, Moon JA, Han JS, Nam CM, Park MS, Kim SK, Chang J, Ahn CM, Kim SK: Validation of the Korean version of the St. George's Respiratory Questionnaire for patients with chronic respiratory disease. Tuberc Respir Dis 2006;61:121–128.

22 Biernacki W, Gould GA, Whyte KF, Flenley DC: Pulmonary hemodynamics, gas exchange, and the severity of emphysema as assessed by quantitative CT scan in chronic bronchitis and emphysema. Am Rev Respir Dis 1989;139:1509–1515.
23 Taguchi O, Gabazza EC, Yoshida M, Yasui H, Kobayashi T, Yuda H, Hataji O, Adachi Y: CT scores of emphysema and oxygen desaturation during low-grade exercise in patients with emphysema. Acta Radiol 2000;41:196–197.
24 Madani A, Keyzer C, Gevenois PA: Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema. Eur Respir J 2001;18:720–730.
25 Gevenois PA, De Vuyst P, de Maertelaer V, Zanen J, Jacobovitz D, Cosio MG, Yernault JC: Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1996;154:187–192.
26 Owens GR, Rogers RM, Pennock BE, Levin D: The diffusing capacity as a predictor of arterial oxygen desaturation during exercise in patients with chronic obstructive pulmonary disease. N Engl J Med 1984;310:1218–1221.
27 Hadeli KO, Siegel EM, Sherrill DL, Beck KC, Enright PL: Predictors of oxygen desaturation during submaximal exercise in 8,000 patients. Chest 2001;120:88–92.
28 Kelley MA, Panettieri RA Jr, Krupinski AV: Resting single-breath diffusing capacity as a screening test for exercise-induced hypoxemia. Am J Med 1986;80:807–812.
29 Mohsenifar Z, Collier J, Belman MJ, Koerner SK: Isolated reduction in single-breath diffusing capacity in the evaluation of exertional dyspnea. Chest 1992;101:965–969.
30 Tylen U, Boijsen M, Ekberg-Jansson A, Bake B, Lofdahl CG: Emphysematous lesions and lung function in healthy smokers 60 years of age. Respir Med 2000;94:38–43.
31 Lee JS, Ra SW, Chae EJ, Seo JB, Lim SY, Kim TH, Lee SD, Oh YM: Validation of the lower limit of normal diffusing capacity for detecting emphysema. Respiration 2011;81:287–293.
32 Garcia-Talavera I, Garcia CH, Macario CC, de Torres JP, Celli BR, Aguirre-Jaime A: Time to desaturation in the 6-min walking distance test predicts 24-hour oximetry in COPD patients with a P_{O_2} between 60 and 70 mm Hg. Respir Med 2008;102:1026–1032.
33 Garcia-Talavera I, Tauroni A, Trujillo JL, Pitti R, Eiroa L, Aguirre-Jaime A, Sanchez A, Abreu J: Time to desaturation less than one minute predicts the need for long-term home oxygen therapy. Respir Care 2011;56:1812–1817.
34 Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, Kazerooni E, Murray S, Criner GJ, Sin DD, Hogg J, Ries AL, Han M, Fishman AP, Make B, Hoffman EA, Mohsenifar Z, Wise R: Sex differences in severe pulmonary emphysema. Am J Respir Crit Care Med 2007;176:243–252.