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(Degree)
博士（保健学）

(Date of Degree)
2019-03-25

(Date of Publication)
2020-03-01

(Resource Type)
doctoral thesis

(Report Number)
甲第7492号

(URL)
https://hdl.handle.net/20.500.14094/D1007492

# 博　士　論　文

**Exercise-Induced Oxygen Desaturation as a Predictive Factor for Longitudinal Decline in 6-Minute Walk Distance in Subjects With COPD**

**（COPD患者における6分間歩行距離の縦断的低下を予測する因子としての酸素飽和度低下）**

平成31年1月17日提出

神戸大学大学院保健学研究科保健学専攻

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# Exercise-induced oxygen desaturation as a predictive factor for longitudinal decline in 6-min walk distance in patients with chronic obstructive pulmonary disease

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**Key words**

chronic obstructive pulmonary disease; peripheral oxygen saturation; 6-min walk test; functional capacity; longitudinal decline; airflow limitation

This paper was published in *Respiratory Care,* 2018 [doi: 10.4187/respcare.06169].

## Abstract

*Background* There are limited longitudinal studies reporting predictive factors for decline in 6-min walk distance (6MWD) in patients with COPD. While previous studies have confirmed the association between airflow limitation (AL) and decline in 6MWD, other factors have not been clarified. The objective of the present study was to investigate whether exercise-induced oxygen desaturation (EID) could be a predictive factor for decline in 6MWD in patients with COPD. The interactive effect of AL on the association between EID and decline in 6MWD was further investigated.

*Methods* A longitudinal observational study was conducted comprising 71 outpatients with COPD who were followed up for 1 year. 6MWD, EID, spirometry, and clinical characteristics were assessed. The effect of EID on changes in 6MWD was examined using linear regression analyses. Furthermore, the subjects were categorized into four groups according to their EID and AL status, and changes in 6MWD were compared among the groups.

*Results* Fifty-one subjects completed the follow-up assessments, and 29 (57%) experienced EID. Multiple linear regression model revealed that EID was the only predictive factor for changes in 6MWD after adjusting for confounders ($\beta = -38.9$, $p < 0.05$). As results of multiple comparisons among the four groups based on EID and AL status, changes in 6MWD in the EID and severe AL group were the lowest.

*Conclusion* Our results revealed that EID is a predictive factor for decline in the functional capacity of patients with COPD. The assessment of EID and AL would thus be useful in estimating the prognosis of decline in the functional capacity of patients with COPD.

## Introduction

Limited functional capacity is the main factor that prevents participation in activities of daily living in patients with chronic obstructive pulmonary disease (COPD).[1] 6-min walk distance (6MWD), the primary outcome of 6-min walk test (6MWT), is the most common tool used to measure the functional capacity of patients with COPD. 6MWD is an important predictive indicator for prognosis independent of some indices of disease severity of COPD, such as airflow limitation (AL) assessed by forced expiratory volume in one second (FEV1) or dyspnea.[2–4] 6MWD naturally decreases over time for patients with COPD,[3–9] and this annual decline in 6MWD also predicts mortality. [4, 5] Therefore, maintaining functional capacity is an important goal in treating patients with COPD, and clarifying the predictive factors for longitudinal decline in 6MWD is warranted.

There are limited longitudinal studies that have reported predictive factors for decline in 6MWD in patients with COPD. Most studies have reported FEV1 as a primary predictive factor.[3, 5–8] Casanova et al.[5] demonstrated that 6MWD decreased only in patients with severe AL (FEV1 <50% predicted) but not in patients with mild AL (FEV1 ≥50% predicted). In addition, previous studies have reported age, sex, body weight, hospitalizations, diffusion capacity, computed tomographic measures of emphysema, hyperinflation, and physical activity as factors associated with decline in 6MWD.[3, 6–9] However, the results have been inconsistent and additional studies are needed to investigate factors to accurately predict longitudinal decline in 6MWD in COPD patients.

Patients with COPD frequently experience significant decreases in oxygen saturation during

exercise owing to the imbalance between oxygen delivery and exercise-induced demand. [10] 6MWT has also been suggested as the preferred tool to identify exercise-induced oxygen desaturation (EID). Some studies have reported that EID occurred in 20%–50% patients with COPD.[10–19] EID negatively affects various organs[20] and is associated with hospitalization and mortality in patients with COPD.[13–15, 18, 19] Nevertheless, the association between EID and decline in 6MWD has not been clarified, especially in longitudinal studies, despite the importance of maintaining functional capacity in COPD patients. We hypothesized that EID would be a factor to cause decline in 6MWD in patients with COPD.

This study aimed to investigate whether EID is associated with longitudinal decline in 6MWD in patients with COPD. Because previous studies have confirmed the association between AL and decline in 6MWD,[3, 5–8] the interactive effect of AL on the association between EID and decline in 6MWD was further investigated in our study.

## Methods

### Subjects

A longitudinal observational study was conducted in outpatients with COPD who were followed up for 1 year. Only those patients who completed the baseline assessment between January 2013 and December 2014 were enrolled in the study. The following inclusion criteria were used to clinically define COPD: presence of symptoms, including cough, sputum production, wheezing, and dyspnea; smoking history (20 pack-years); existence of emphysema on chest computed tomography and a physician diagnosis of COPD.[21–23] The exclusion criteria were as follows: history of lung surgical procedures, comorbidity of other lung diseases (e.g. interstitial lung disease, lung tuberculosis, pneumoconiosis, or lung cancer), exacerbation-related hospitalization 3 months before baseline assessment, and neuromuscular conditions that would interfere with 6MWT. This study was approved by the ethics committee of Kobe University (N287). All subjects provided written or verbal informed consent according to the ethical standards set forth in the declaration of Helsinki.

### 6-min walk test

6MWT was performed according to the American Thoracic Society (ATS) guidelines at baseline and after a 1-year follow-up.[24] The test was performed once each time, and a practice test was not conducted. The test was supervised by a trained physical therapist, in a location where a

rapid, appropriate response to an emergency was possible. No adverse events occurred during the test. The subjects were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt able to do so. The total distance walked was recorded as 6MWD. 6MWD was used as the primary outcome measure of functional capacity. Modified Borg scale (mBorg) was used to record symptom scores for dyspnea during the test. Peripheral oxygen saturation ($SpO_2$) and pulse rate during 6MWT were continuously recorded using a pulse oximeter (WristOx 3150; Nonin Medical, Plymouth, MN, USA) with a finger probe and an analysis software (WristOx 2; Star Product, Tokyo, Japan). EID was defined as a nadir $SpO_2$ level of <90% or $\Delta SpO_2$ level of ≥4%.[12, 15]

**Clinical characteristics**

A chest physician performed physical examination at baseline assessment. Demographic information was collected, including body weight, height, medical histories, applied inhaled drugs, and with or without long-term oxygen treatment. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m) and is therefore expressed as $kg/m^2$. Dyspnea was measured using the modified Medical Research Council (mMRC) dyspnea scale. The COPD Assessment Test (CAT) was used to assess the disease-specific quality of life. Post-bronchodilator spirometry was conducted using an Autospirometer System 21 (Minato Medical Science, Osaka, Japan). The following values were obtained: FEV1, forced vital capacity (FVC), and FEV1/FVC ratio. Diffusing lung capacity was also measured as diffusion lung capacity for carbon monoxide

(DLCO) by assessing single-breath carbon monoxide uptake. Based on FEV1 values, predicted values of mild and severe AL were defined as ≥ 50% (Global Initiative for Chronic Obstructive Lung Disease; GOLD 1 or 2) and < 50% (GOLD 3 or 4), respectively.

**Statistical analysis**

All statistical analyses were performed using a commercially available software (JMP9.0 J; SAS Institute Japan, Tokyo, Japan). Data are presented as mean ± standard deviation (SD) or proportion (%), as appropriate. Using independent *t*-tests or chi-square tests, patient characteristics and 6MWD at baseline and other measures of 6MWT were compared. To assess the effect of EID or AL on changes in 6MWD over time, repeated measures two-way analyses of variance (ANOVA) were performed. Furthermore, the value of longitudinal changes in 6MWD was calculated for over 1 year, and linear regression analyses were performed to explore the independent predictive factors for changes in 6MWD. Single linear regressions were performed for the unadjusted model using longitudinal changes in 6MWD as a dependent variable and EID and potential confounders, which were considered theoretically related to outcome (age, sex, BMI, smoking history, mMRC, CAT score, exacerbations during follow-up, FEV1, FVC, and DLCO), as independent variables. Then, a multiple linear regression was performed for the adjusted model using longitudinal changes in 6MWD as a dependent variable and EID as an independent variable. Sex and age were mandatorily

included in the model. Covariates associated with decline in 6MWD ($p < 0.20$) were also included. Furthermore, the subjects were categorized into four groups based on EID and AL status (i.e., non-EID and mild AL, non-EID and severe AL, EID and mild AL, and EID and severe AL groups). The linear trend of longitudinal changes in 6MWD across the groups was determined using a Jonckheere–Terpstra trend test. The level of significance for all analyses was set at $p < 0.05$.

## Results

A flow diagram of subjects from baseline to follow-up is shown in Figure 1. Of the 71 outpatients with COPD who completed baseline assessments and were included in this study, 51 (71.8%) were able to perform 6MWT at follow-up. The mean follow-up period was 365 ± 30 days. Twenty subjects had missing data on 6MWD after 1 year and were lost to follow-up. No patient died during the follow-up period. Ten patients experienced one or more exacerbations.

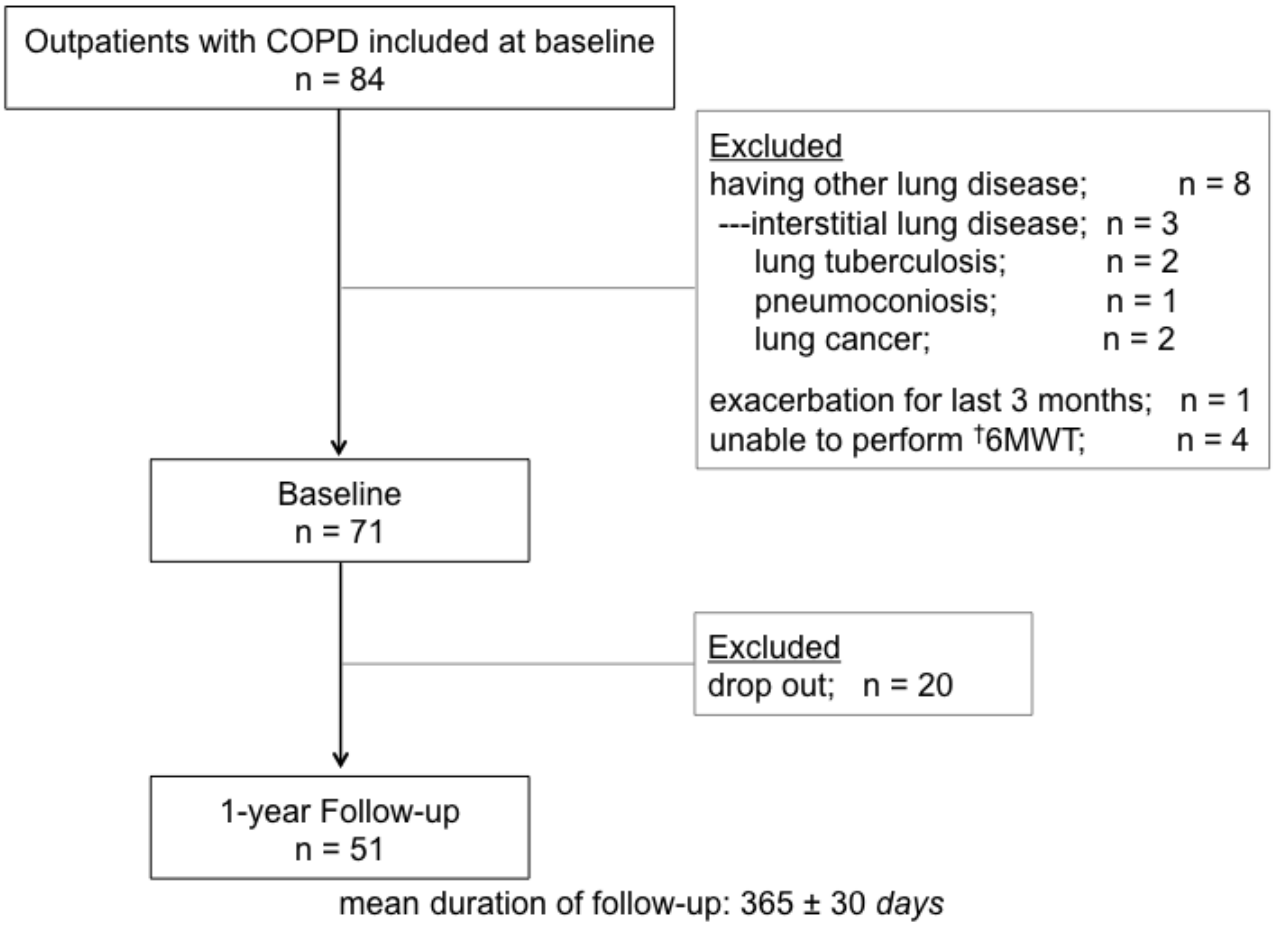


**Figure 1** Flow diagram of patients with chronic obstructive pulmonary disease (COPD) enrolled in the study

†*6MWT* 6-min walk test

Baseline characteristics of the subjects are summarized in Table 1. Overall, 56.9% of the subjects experienced EID during 6MWT. There were no significant differences in EID status among age, sex, BMI, and smoking history. Subjects with EID were more likely to report higher frequency of dyspnea in mMRC scale than those without EID ($p = 0.01$). Furthermore, they had poor quality of life according to CAT score ($p = 0.05$). All patients had used some type of inhalation medication (long-acting muscarinic antagonist, long-acting $\beta_2$ agonist, or inhaled corticosteroid), and there were no significant differences in type of medication used based on EID occurrence. Subjects with EID had significantly lower pulmonary functions, including FEV1 and FVC ($p = 0.005$, $p = 0.03$, respectively). More subjects with EID had severe AL than those without EID ($p = 0.02$). When comparing 6MWT measures among the groups, no differences were found between the EID and non-EID groups in 6MWD (EID group, 400 ± 130 m vs. non-EID group, 440 ± 81 m), highest pulse ratio, and dyspnea at baseline and during the test.

**Effect of EID and AL on longitudinal decline in 6MWD**

The mean ± SD of longitudinal changes in 6MWD over 1 year was −19 ± 55 m. Repeated measures two-way ANOVA revealed a significant interaction between decline in 6MWD and EID ($F = 8.7$, $p = 0.005$) (Figure 2-A). The EID group exhibited a significant decline in 6MWD (mean change: −38 ± 50 m), whereas the non-EID group did not. A significant interaction was also found

**Table 1.** Baseline characteristics and 6MWT measures in patients with COPD based on EID status

| Variables | EID group (n = 29, 56.9%) | Non-EID group (n = 22, 43.1%) | *p* value |
|---|---|---|---|
| Age, *years* | 72.7 ± 8.9 | 70.0 ± 7.3 | .26 |
| Male, *n (%)* | 24 (82.8) | 16 (72.7) | .50 |
| Smoking history, *pack-years* | 50.8 ± 30.1 | 60.5 ± 42.1 | .34 |
| BMI | 22.6 ± 4.4 | 21.7 ± 4.5 | .47 |
| mMRC dyspnea scale | 2.25 ± 0.65 | 1.76 ± 0.62 | .01 |
| CAT score | 17.3 ± 7.3 | 12.7 ± 8.7 | .05 |
| Inhalation medicine, *n (%)* | | | |
| Long-acting muscarinic antagonist | 24 (82.8) | 19 (86.4) | > .99 |
| Long-acting $\beta_2$ agonist | 18 (62.1) | 18 (81.8) | .21 |
| Inhaled corticosteroid | 7 (24.1) | 8 (36.4) | .37 |
| LTOT, *n (%)* | 3 (10.3) | 1 (4.6) | .62 |
| Baseline spirometry | | | |
| FEV1, *% predicted* | 51.1 ± 17.9 | 67.1 ± 20.9 | .005 |
| FVC, *% predicted* | 74.1 ± 16.9 | 84.3 ± 15.8 | .03 |
| FEV1/FVC ratio, *%* | 54.4 ± 13.6 | 65.9 ± 11.3 | .002 |
| DLCO, *% predicted* | 49.3 ± 24.3 | 60.8 ± 23.6 | .10 |
| GOLD classification, *n (%)* | | | .08 |
| Stage I | 2 ( 6.9) | 5 (22.7) | |
| Stage II | 12 (41.4) | 13 (59.1) | |
| Stage III | 12 (41.4) | 3 (13.6) | |
| Stage IV | 3 (10.3) | 1 ( 4.6) | |
| AL status, *n (%)* | | | .02 |

| | | | |
|---|---|---|---|
| Mild AL (FEV1 ≥50% predicted value) | 14 (48.3) | 18 (81.8) | |
| Severe AL (FEV1 <50% predicted value) | 15 (51.7) | 4 (18.2) | |
| Baseline 6MWT | | | |
| 6MWD, *m* | 400 ± 130 | 440 ± 81 | .22 |
| Baseline $SpO_2$, *%* | 95.7 ± 1.7 | 96.3 ± 1.5 | .17 |
| Lowest $SpO_2$, *%* | 88.5 ± 3.0 | 94.0 ± 1.9 | < .001 |
| $\Delta SpO_2$, *%* | 7.2 ± 2.9 | 2.3 ± 1.0 | < .001 |
| Baseline pulse ratio, *beats/min* | 79 ± 14 | 79 ± 12 | .86 |
| Highest pulse ratio, *beats/min* | 109 ± 14 | 107 ± 11 | .55 |
| Baseline Dyspnea, *mBorg* | 0.3 ± 0.6 | 0.1 ± 0.3 | .20 |
| Highest Dyspnea, *mBorg* | 3.6 ± 3.0 | 2.2 ± 2.1 | .06 |

Data are presented as mean ± standard deviation or proportion (%), as appropriate.
EID = exercise-induced oxygen desaturation, BMI = body mass index
mMRC = modified Medical Research Council
CAT = COPD Assessment Test
LTOT = long-term oxygen treatment
FEV1 = forced expiratory volume in one second
FVC = forced vital capacity
DLCO = diffusion lung capacity for carbon monoxide
AL = airflow limitation
6MWT = 6-min walk test
6MWD = 6-min walk distance
$SpO_2$ = peripheral oxygen saturation
mBorg = modified Borg scale

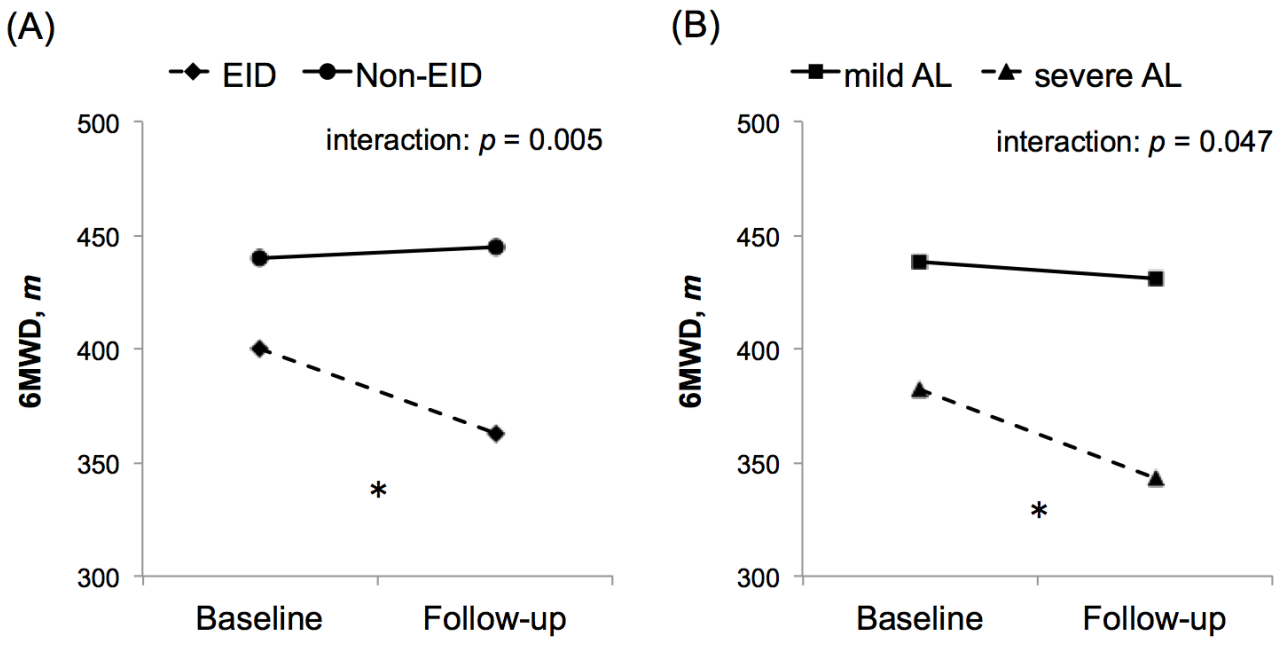


**Figure 2** Changes in 6-min walk distance (6MWD) from baseline to 1-year follow-up based on exercise-induced oxygen desaturation (EID) (**A**) and airflow limitation (AL) (**B**)

* $p < 0.01$

between decline in 6MWD and AL status ($F = 4.1$, $p = 0.047$) (Figure 2-B). The severe AL group exhibited a significant decline in 6MWD (mean change: −39 ± 56 m), whereas the mild AL group did not.

The unadjusted linear regression analysis demonstrated that EID and FVC were significantly associated with longitudinal changes in 6MWD ($p = 0.005$, $p = 0.02$, respectively). FEV1 tended to be associated with longitudinal changes in 6MWD ($p = 0.10$). In the adjusted analysis, EID, FEV1, FVC, sex, and age were included in the multiple linear regression model as dependent variables, and EID was the only predictive factor for decline in 6MWD ($\beta = -38.9$, $p = 0.02$) (Table 2).

**Table 2.** Linear regression models to predict longitudinal changes in 6MWD over 1 year

| | Single regression | | Multiple regression * | |
|---|---|---|---|---|
| Dependent variables | β coefficient | *p* value | β coefficient | *p* value |
| EID (reference, non-EID) | −42.8 | .005 | −38.9 | .02 |
| Age, *years* | −0.6 | .52 | 0.3 | .76 |
| Male (reference: female) | −9.2 | .63 | 0.3 | .99 |
| Smoking history, *pack-years* | 0.0 | .73 | | |
| BMI | −1.1 | .55 | | |
| mMRC dyspnea scale | −9.6 | .43 | | |
| CAT score | −1.1 | .26 | | |
| Exacerbations during follow-up (reference, no exacerbation) | 1.4 | .94 | | |
| FEV1, *% predicted* | 0.6 | .10 | −0.5 | .41 |
| FVC, *% predicted* | 1.1 | .02 | 1.2 | .08 |
| DLCO, *% predicted* | 0.1 | .68 | | |
| Baseline 6MWD, *m* | 0.0 | .72 | | |

* $R^2$ value for multiple regression model was 0.13.

6MWD = 6-min walk distance
EID = exercise-induced oxygen desaturation
BMI = body mass index
mMRC = modified Medical Research Council
CAT = COPD Assessment Test
FEV1 = forced expiratory volume in one second
FVC = forced vital capacity
DLCO = diffusion lung capacity for carbon monoxide

**Comparison of longitudinal changes in 6MWD within the four groups based on EID and AL status**

Based on EID and AL status, 18 subjects (35.3%) were categorized into non-EID and mild AL group, 4 subjects (7.8%) into non-EID and severe AL group, 14 subjects (27.5%) into EID and

mild AL group, and 15 subjects (29.4%) into EID and severe AL group. Longitudinal changes in 6MWD showed a significant linear trend across the groups using the Jonckheere–Terpstra trend test ($p = 0.007$). Changes in 6MWD in EID and severe AL group (mean change: −50 ± 49 m) was the lowest (Figure 3).

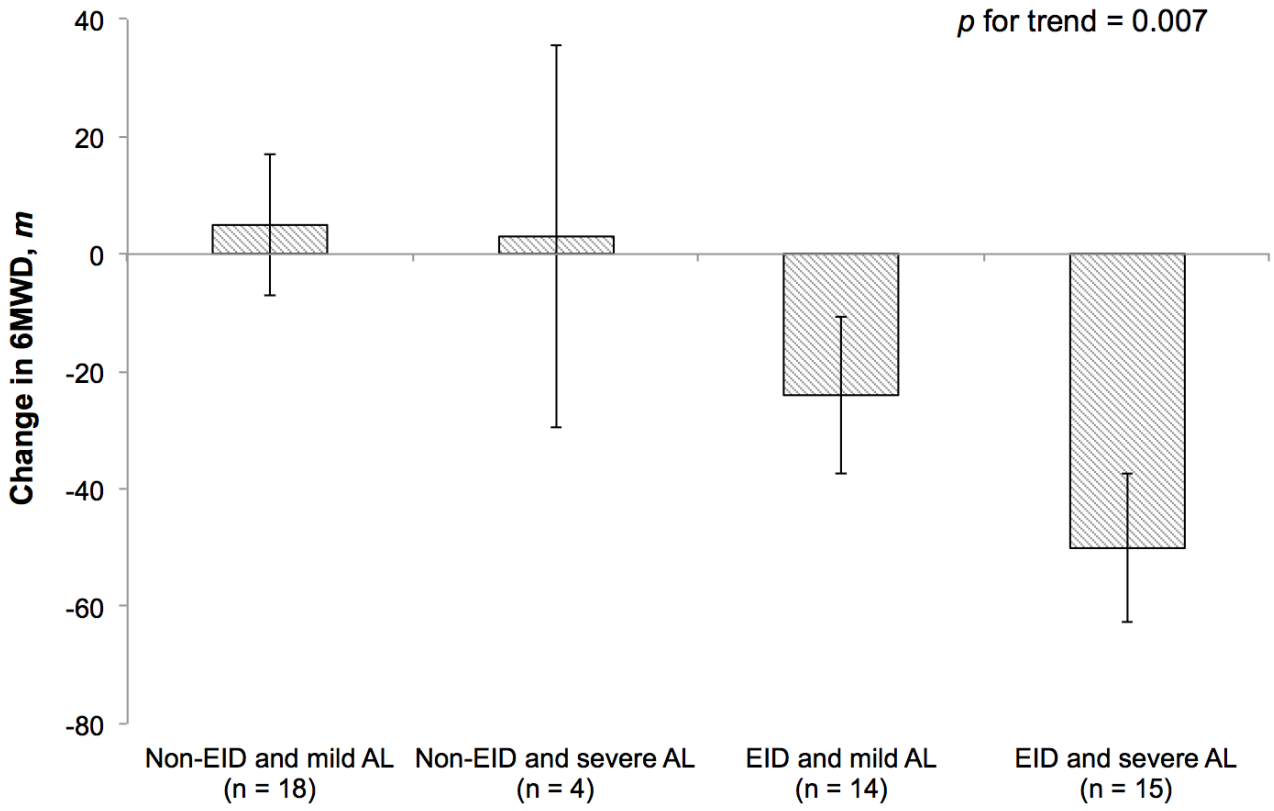


**Figure 3** Changes in 6-min walk distance (6MWD) from baseline to 1-year follow-up between the groups based on the exercise-induced oxygen desaturation (EID) and airflow limitation (AL) status The linear trend across the groups was determined using the Jonckheere–Terpstra trend test.

## Discussion

This longitudinal study revealed that subjects with COPD who experienced EID during 6MWT had a significant decline in 6MWD after a 1-year follow-up but did not change in subjects without EID. EID was the significant predictive factor for decline in 6MWD after adjusting for potential confounders, including age, sex, FEV1 (AL), and FVC. In addition, our results indicated that subjects with EID combined with severe AL had the largest decline in 6MWD.

The mean decline in 6MWD in subjects with COPD after the 1-year follow-up was 19 m, which increased to 38 m, particularly in subjects with EID. Some studies demonstrated that 6MWD in patients with COPD naturally decreases over time, and the annual decline was reported as 2–40 m,[3–9] which was comparable to that of the current study. The larger decline in 6MWD was related to unfavorable outcomes,[3, 4] and the minimally clinical important difference (MCID) for 6MWD was proposed as >30 m.[25, 26] Polkey et al.[27] demonstrated that when decline in 6MWD exceeded MCID (i.e., 30 m), the patient had an increased risk for mortality. Decline in 6MWD in subjects with EID exceeded the MCID, which suggested that EID had a high impact on the functional capacity of patients with COPD.

To the best of our knowledge, this is the first study to report that EID is a significant predictive factor for decline in 6MWD. Importantly, a longitudinal association was observed even after adjustment for AL, a confirmed predictive factor, and for other potential confounders. Several studies have demonstrated that EID is associated with longitudinal decline in lung function, lean body mass, and quality of life.[12, 15] Furthermore, patients with COPD experiencing EID had increased risk of

exacerbation and mortality.[13–15, 18, 19] Waatevik et al.[15] studied 370 patients with COPD for 3 years and found that those with EID had an approximately two-fold increased risk of mortality and a 50% increased risk for experiencing future exacerbations. Owing to the importance of functional capacity of patients with COPD, our results support and confirm EID as a noteworthy symptom in COPD. A recent large randomized control trial demonstrated that long-term treatment with supplemental oxygen did not provide any benefit with respect to the time to death or first hospitalization or any sustained benefit among patients with COPD experiencing moderate EID.[28] These patients might need intervention to enhance their functional capacity.

There are several explanations for the association between EID and decline in functional capacity. First, dyspnea evoked by EID might cause limited physical activity and deconditioning. Hypoxemia is one of the contributing factors for dyspnea, which is caused by stimulating the chemoreceptor in the carotid and aortic bodies.[29] In our study, subjects with EID complained of severe dyspnea than those without EID. Dyspnea, a sensation of breathlessness, is a major reason for limited physical activity in patients with COPD and leads to decline in physical and cardiopulmonary function.[1] Second, the negative effects of chronic hypoxemia might cause decline in functional capacity. Patients who experienced EID during 6MWT were also shown to experience these symptoms in activities of daily living, both during physical activity and sleep.[30, 31] Chronic hypoxemia induces pulmonary hypertension, polycythemia, systemic inflammation, and skeletal muscle dysfunction,[20] and these adverse sequelae in various organs are correlated with functional

capacity. However, these statuses (e.g., physical activity, pulmonary arterial pressure, or muscle function) were not assessed, and further studies are warranted to clarify these relationships.

We also found that decline in 6MWD was the largest in subjects with EID combined with severe AL (mean annual decline: 50 m). Another originality of the present study is that the combined assessment of AL and EID enabled a more sensitive prediction for declines in the functional capacity of patients with COPD compared with the assessment of only AL. Our results were consistent with those of previous studies,[3, 5–7] wherein 6MWD decreased in patients with severe AL but not in patients with mild AL. In addition, our results indicated that EID predicted decline independent of the severity of AL and that EID had an interactive effect with AL on decline in functional capacity. Causes of EID are multifactorial, such as ventilation–perfusion mismatching, diffusion-type limitation, shunting, and reduced oxygen content of mixed venous blood, all contributing to EID to some extent.[32] EID in COPD is associated with not only severe AL but also other various symptoms, such as decreasing diffusing capacity, larger emphysema, dynamic hyperinflation, pulmonary artery enlargement, poorer muscle strength, and impaired daily physical activity.[11, 12, 16, 17, 33] Therefore, the assessment of EID would represent different aspects of disease severity of COPD apart from AL. This assessment is noninvasive and easily practiced and might be a more informative and appropriate method when combined with the assessment of AL during the first screening of disease severity in patients with COPD.

This study has some limitations. First, the number of subjects was inadequate to generalize our results. Second, important factors previously demonstrated to be associated with decline in

6MWD, such as physical activity, lower limb strength, hyperinflation, and computed tomographic measures of emphysema, were unaccounted for[6–8] because data regarding these factors were not collected at baseline. This also limited the generalizability of the results. Future studies with a larger sample size investigating these factors associated with decline in 6MWD, including the potential confounding factors, are needed. Third, 6MWT was performed only once on each occasion in the present study, although the ATS guidelines recommend two tests.[24] As the learning effect could occur in measuring 6MWD,[34] the annual decline might be underestimated in only one measurement. Nevertheless, subjects with COPD experiencing EID demonstrated a larger decline in their 6MWD; therefore, this finding is considered relevant.

## Conclusions

Our results revealed that EID was a predictive factor for decline in the functional capacity of patients with COPD, particularly EID combined with severe AL. The assessment of EID and AL would thus be useful in estimating the prognosis of decline in the functional capacity of patients with COPD.


## Acknowledgments

The authors would like to thank Ryuichi Sawa, Satoshi Minami, Yuya Ueda, Tatsuro Inoue, Katsuyoshi Tanaka, Ryo Nakamura, Shunsuke Murata, Takashi Saito, Taiki Sugimoto, Tsunenori Isa, Aoi Ebina, Yuki Kondo, Yamato Tsuboi, Kazufumi Kitagaki, Kotaro Tosizawa, and Shoma Fukuta of the Department of Community Health Sciences, Kobe University Graduate School of Health Sciences, for their constructive comments on the design of this study and interpretation of the data analysis. The authors would also like to thank Enago (www.enago.jp) for the English language review.

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