

Effects of pharmacologic treatment based on airflow limitation and breathlessness on daily physical activity in patients with chronic obstructive pulmonary disease

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Background: Improvement in the daily physical activity (PA) is important for the management of chronic obstructive pulmonary disease (COPD). However, the effects of pharmacologic treatment on PA are not well understood. We evaluated the effects of additional medications, including bronchodilator with or without inhaled corticosteroid, based on airflow limitation and breathlessness on the PA in COPD patients and the factors that could predict or affect the improvement in PA.

Methods: A prospective non-randomized observational study was employed. Twenty-one COPD subjects without any other diseases that might reduce PA were recruited. The PA was measured with a triaxial accelerometer for 2 weeks, and pulmonary function tests and incremental shuttle walking tests were administered before and after 4-week treatment with an additional medication.

Results: Bronchodilation was obtained by additional medication. The mean values of PA evaluated by metabolic equivalents (METs) at ≥ 3.0 METs and the duration of PA at ≥ 3.0 METs and ≥ 3.5 METs were improved by medication. The % change in the duration of PA at ≥ 3.5 METs was significantly correlated with the baseline functional residual capacity (FRC), residual volume, and inspiratory capacity/total lung capacity. However, the % change in the duration of PA at any intensity was not correlated with the % changes of any values of the pulmonary function tests or incremental shuttle walking test except the PA at ≥ 2.5 METs with FRC.

Conclusion: Medication could improve the PA in patients with COPD, especially at a relatively high intensity of activity when medication was administered based on airflow limitation and breathlessness. The improvement was seen in the patients with better baseline lung volume, but was not correlated with the improvements in the pulmonary function tests or exercise capacity.

Keywords: COPD, accelerometer, bronchodilator, pulmonary function, predictor

Introduction

The daily physical activity (PA) is reduced in patients with chronic obstructive pulmonary disease (COPD) compared to healthy subjects.¹⁻⁶ As the PA is related to the decline of lung function,⁷ hospitalizations,^{8,9} and mortality¹⁰ and is a factor reflecting the highest relative risk of death in COPD,¹¹ the maintenance or improvement in PA is an important target for the management of COPD.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of long-acting bronchodilator (BD), such as anticholinergics, beta-2-adrenoceptor agonists, and in some cases, inhaled corticosteroid (ICS), for the

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management of stable COPD patients.¹² There have been only a few reports about the effect of BD on PA. In some reports, BD, especially indacaterol^{13,14} and aclidinium,¹⁵ improved PA, but in other reports, BD, especially indacaterol^{16,17} and tiotropium,¹⁸ did not. BD can improve exercise capacity,^{19,20} but it is still unclear whether BD can improve the daily PA in patients with COPD. GOLD also recommends that COPD patients should be assessed using risk factors (airflow limitation or exacerbation) and symptoms or breathlessness for the management.¹²

We evaluated the effects of additional pharmacologic treatment based on airflow limitation and breathlessness on the PA in patients with COPD monitored using an Actimarker® (Panasonic, Osaka, Japan), a compact-sized, well-validated, triaxial accelerometer.²¹ Furthermore, we also evaluated the physiological factors that could predict or affect the improvement in PA.

Subjects and methods

Subjects

Stable COPD patients, aged 50 or older and recruited from among the outpatients of Wakayama Medical University Hospital, were either not using a BD or were taking a long-acting muscarinic antagonist (LAMA) or a long-acting beta-2 adrenergic agonist (LABA), but not both. Patients using oxygen therapy or suffering from other diseases that might reduce PA and patients who received respiratory rehabilitation within 6 months before the entry were excluded. COPD was diagnosed as post-BD forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) <0.7. The patients did not have any other pulmonary diseases such as asthma or bronchiectasis.¹²

Protocol

Patients wore an Actimarker® the whole day, except while bathing, for 2 weeks and performed pulmonary function tests and incremental shuttle walking test (ISWT) on the last day of the PA measurement. They were additionally treated with medication and then evaluated for their PA after

4–6 weeks from the beginning of treatment and performed pulmonary function tests and ISWT on the last day of the PA measurement. The effects of medication on PA and other parameters were evaluated. Then, in order to determine if there were some predictable factors that could improve PA by pharmacologic treatment, % change in PA was compared with the baseline physiological parameters. Furthermore, in order to evaluate the factors that could affect the improvement in PA, % change in PA was compared with % change in physiological parameters.

Written informed consent was obtained from all participants, and the study was approved by the local ethics committee (Committee: IRB Committee of Wakayama Medical University, approval number: 968, approval date: May 30, 2011; Clinical Trial Registration: UMIN, registration number: UMIN000006293, registration date: September 15, 2011 [<http://www.umin.ac.jp>]).

Selection of BD

Which type of additional medication was decided according to the GOLD stage, the Modified Medical Research Council (MMRC) dyspnea scale, and the baseline treatment. The details are presented in Table 1. Briefly, 1) in cases of stage 1 or 2, MMRC 0 or 1 (group A in GOLD classification), and no BD treatment at baseline, the final treatment was either LAMA or LABA; 2) in cases of stage 1 or 2, MMRC 2 or more (group B in GOLD), and no BD; in cases of stage 1 or 2, any MMRC (group A or B in GOLD), and one BD; and in cases of stage 3 or 4, MMRC 0 or 1 (group C in GOLD), and no or one BD, the final treatment was both LAMA and LABA; and 3) in cases of stage 3 or 4, MMRC 2 or more (group D in GOLD), and no or one BD, the final treatment was both LAMA and ICS/LABA combination. The kind of additional LABA was salmeterol 50 µg twice daily or tulobuterol hydrochloride patch 2 mg once a day, the LAMA was tiotropium HandiHaler 18 µg once a day, and the ICS/LABA combination was fluticasone propionate 250 µg with salmeterol 50 µg twice daily or budesonide 320 µg with formoterol fumarate dehydrate 9 µg twice daily.

Table 1 Criteria for selection of bronchodilator

GOLD stage	MMRC scale	Baseline treatment	Final treatment	No of patients
1 or 2	0–1	None	LAMA or LABA	5
1 or 2	2–4	None	LAMA + LABA	3
1 or 2	Any	LAMA or LABA	LAMA + LABA	6
3 or 4	0–1	None or LAMA or LABA	LAMA + LABA	3
3 or 4	2–4	None or LAMA or LABA	LAMA + ICS/LABA	4

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; MMRC, Modified Medical Research Council; None, no bronchodilator; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-2 adrenergic agonist; ICS, inhaled corticosteroid.

Assessment of PA

The Actimarker[®] is a small (74.5 mm × 13.4 mm × 34.0 mm) and lightweight (36.0 g) triaxial accelerometer that is worn only at the waist and that can continuously monitor activity for over 1 month. It collects the data of triaxial acceleration at 20 Hz, and the standard deviation of the data for 1 minute is defined as the mean value of acceleration. The value of metabolic equivalents (METs) is calculated from the linear regression formula produced by the relationship between the mean value of acceleration and the METs measured using a respiratory gas metabolic system.^{22,23} Actimarker[®] has already been validated for evaluating the PA of COPD in terms of the intensities.²¹

The detection of reproducible data is very important for the evaluation of PA because PA can easily fluctuate day by day. As the PA in COPD could be suppressed on a rainy day²¹ or holiday,^{24,25} the data of these days should be excluded to obtain reproducible data. The recommended number of measurement days in most of the previous reports was 3–5.^{1,24–26} In the case of Actimarker[®], we have reported it to be 3.²¹ Therefore, in order to obtain a representative value of the daily PA, we excluded the data of rainy days, weekend days, and holidays and also excluded the data of the first and last days because data of a whole day were not obtained. Finally, we accepted the data of the first 3 full days from among the included days of the 2 weeks. The mean values of the duration of PA from the extracted 3 days were employed as the representative PA in the patients with COPD.

Assessment of physiological properties

The lung function was evaluated by CHESTAC-8800 DN type (Chest Ltd., Tokyo, Japan) according to the recommendations of the American Thoracic Society/European Respiratory Society.²⁷ ISWT was performed according to Singh's method (Japanese license number: 410).²⁸

Statistical analysis

Analyses were performed using GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA). Paired *t*-test was used for the comparisons of pulmonary functions and ISWT before and after treatment. Wilcoxon signed-rank test was used for the comparisons of PA before and after treatment. One-way analysis of variance (ANOVA) was used for finding the % change in PA among the different intensities of PA. Spearman's correlation was used for the relationship between % change in PA and baseline values of ISWT or pulmonary function tests by treatment, and between % change

in PA and % change in pulmonary function tests or ISWT by treatment. Comparisons were considered significant for *P*-values of less than 0.05.

Results

The numbers of patients with stages I, II, III, and IV were 4, 10, 4, and 3, respectively, and those with MMRC 0, 1, 2, 3, and 4 were 7, 7, 5, 2 and 0, respectively (Table 2). The numbers of patients in groups A, B, C, and D of GOLD classification were 10, 4, 4, and 3, respectively. At baseline, eleven patients received no BD, nine received LAMA, and one received LABA. Finally, five patients received either LAMA or LABA, 12 both LAMA and LABA, and four both LAMA and ICS/LABA combination (Table 1).

After pharmacologic treatment, vital capacity, inspiratory capacity (IC), FVC, FEV₁, residual volume (RV), and ISWT were significantly improved, and the changes in the mean values of IC, FEV₁, and ISWT were 0.14 L, 0.14 L, and 35 m, respectively (Table 3), suggesting that effective bronchodilation had been obtained. The PA level evaluated by the values of the summation of METs multiplied by hours (METs·hr) at ≥3.0 METs was significantly improved (*P*=0.02) (Figure 1). The durations of activity were improved at intensities ≥3.0 METs and ≥3.5 METs, but not at ≥2.0

Table 2 Characteristics of patients

Sex (M/F)	21/0
Age (years)	70.7±7.7
BMI (kg/m ²)	21.3±3.3
Smoking	
Cur/Ex/Non	6/15/0
Pack-year	63.7±31.1
MMRC scale (0/1/2/3/4)	7/7/5/2/0
Staging (I/II/III/IV)	4/10/4/3
Pulmonary function	
FVC (L)	3.50±0.65
FEV ₁ (L)	1.72±0.63
FEV ₁ % (%)	48.2±13.3
FEV ₁ % predicted (%)	59.8±21.7
IC (L)	2.13±0.37
IC/TLC (%)	33.3±6.4
FRC (L)	4.32±0.81
RV (L)	2.84±0.62
TLC (L)	6.47±0.85
DLCO (mL/min/mmHg)	14.87±5.16
DLCO/VA (mL/min/mmHg/L)	3.24±1.15

Abbreviations: BMI, body mass index; Cur, current smoker; Ex, ex smoker; Non, nonsmoker; MMRC, Modified Medical Research Council; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEV₁%, 100 × FEV₁/FVC; FEV₁% predicted, 100 × FEV₁/predicted FEV₁; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; DLCO, pulmonary carbon monoxide diffusing capacity; min, minute; VA, alveolar volume.

Table 3 Effects of medication on pulmonary function tests and ISWT

Variables	Pre	Post	P-value
VC (L)	3.58±0.65	3.76±0.63	0.007
IC (L)	2.13±0.37	2.27±0.35	0.001
FVC (L)	3.50±0.65	3.63±0.55	0.008
FEV ₁ (L)	1.72±0.63	1.86±0.58	0.001
FRC (L)	4.32±0.81	4.24±0.85	0.249
RV (L)	2.84±0.62	2.67±0.61	0.015
TLC (L)	6.47±0.85	6.46±0.97	0.936
DLCO (mL/min/mmHg)	14.87±5.16	14.61±5.15	0.293
DLCO/VA (mL/min/mmHg/L)	3.24±1.15	3.20±1.15	0.438
ISWT (m)	464.7±118.0	499.4±108.7	0.033

Abbreviations: ISWT, incremental shuttle walking test; VC, vital capacity; IC, inspiratory capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLCO, pulmonary carbon monoxide diffusing capacity; VA, alveolar volume; min, minute.

METs and ≥ 2.5 METs (Figure 2). Three patients at ≥ 3.0 METs and five patients at ≥ 3.5 METs improved their PA by more than 100%. Among these patients, only one patient improved at both intensities and the others improved only at one of the intensities. Furthermore, eight patients at ≥ 3.0 METs and five patients at ≥ 3.5 METs improved their PA by more than 50%, and numerically, 15 of 21 patients (71.4%) improved at ≥ 3.0 METs and 16 (76.2%) improved at ≥ 3.5 METs (Figure 3). The mean value of the % change in PA was increased as the intensity of activity increased, but the difference was not statistically significant by one-way ANOVA ($P=0.193$) (Figure 3).

The % change in PA at ≥ 3.5 METs by medication was correlated with the baseline values of functional residual capacity (FRC), RV, and IC/total lung capacity (TLC), and the % change in PA at ≥ 3.0 METs was correlated with the

baseline values of FVC (Table 4). Although the % change in PA at ≥ 2.5 METs by medication was weakly correlated only with the % change in FRC, the % changes in PA at other intensities were not correlated with the % changes in any pulmonary function tests or ISWT (Table 5).

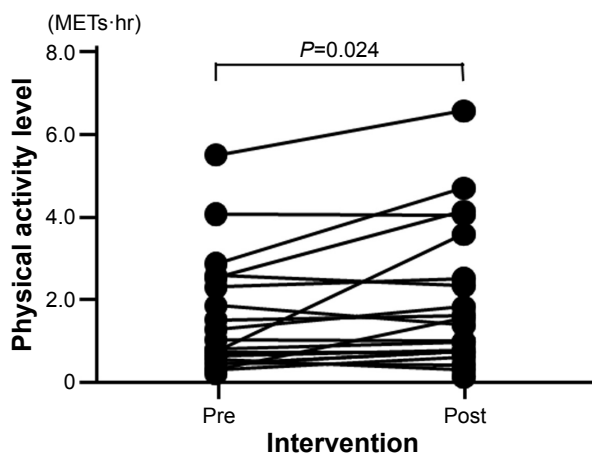
Discussion

We demonstrated that pharmacologic treatment significantly improved the PA at a relatively high intensity in patients with COPD when medication was administered based on airflow limitation and breathlessness. The degree of the improvement in PA at ≥ 3.5 METs was correlated with the baseline pulmonary function, but was not correlated with the degree of improvement in pulmonary function or ISWT.

Pharmacologic treatment improved the PA level (METs·hr) and the duration of PA. Hataji et al¹³ and Watz et al¹⁴ reported that indacaterol improved PA, and Beeh et al¹⁵ reported that acclidinium improved PA, which were compatible with our results. However, O'Donnell et al¹⁶ and Nishijima et al¹⁷ reported that indacaterol did not improve PA and Troosters et al¹⁸ reported that tiotropium did not improve PA. The differences in these reports might be caused by differences in several factors, including the index of PA, the duration of medication, the kind of accelerometers, the conditions of data collection, and also the distribution of airflow limitation or breathlessness of patients.

In the current study, we selected additional medication based on airflow limitation, breathlessness, and baseline treatment of BD, which is in accordance with the GOLD recommendations¹² and a realistic approach to treatment. In all the previous reports,^{13–18} the effects of BD were evaluated without taking into account breathlessness or airflow limitation. This might be one of the reasons for the difference in their results.

We recruited patients with both no and one BD at baseline. Among the patients who improved their PA by more than 100% at ≥ 3.0 METs (three patients) or ≥ 3.5 METs (five patients), two patients received no BD at baseline (two of eleven patients with no BD), one patient received one BD (one of ten patients with one BD) at ≥ 3.0 METs ($P=0.593$ with chi-square test), three patients received no BD (three of eleven), and two patients received one BD (two of ten) at ≥ 3.5 METs ($P=0.696$). Among the patients who improved their PA by more than 50% at ≥ 3.0 METs (five patients) or ≥ 3.5 METs (eight patients), three patients received no BD (three of eleven) and two received one BD (two of ten) at ≥ 3.0 METs ($P=0.696$) and five received no BD (five of eleven) and three received one BD (three of ten) at ≥ 3.5 METs ($P=0.466$). Though the rate of improvement in patients

**Figure 1** Effect of medication on the PA level.

Abbreviations: PA, physical activity; METs·hr, metabolic equivalents multiplied by hours.

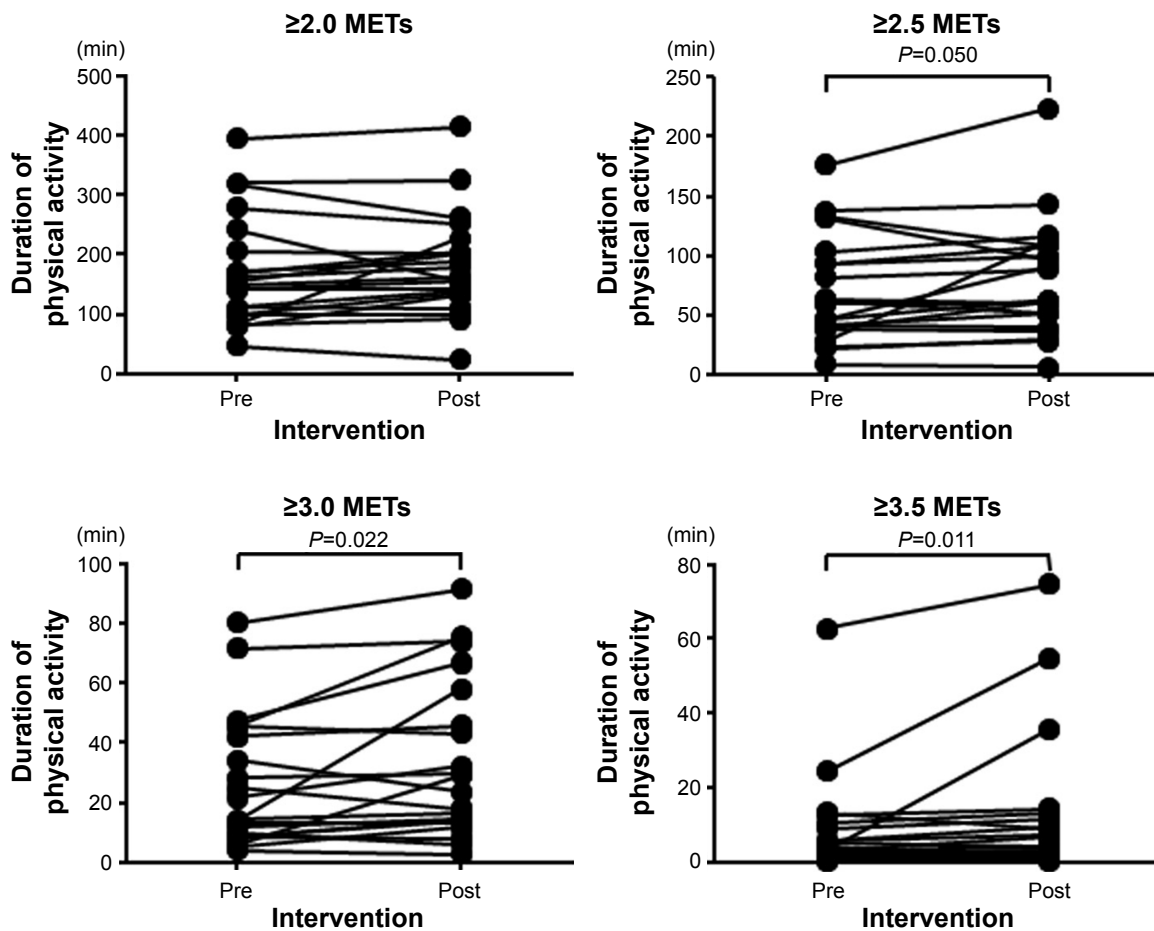


Figure 2 Effects of medication on the duration of PA.
Abbreviations: PA, physical activity; METs, metabolic equivalents; min, minutes.

with no BD was numerically higher than the patients with one BD at the baseline, there was no significant difference between the two groups.

Concerning the index of PA, in addition to the current study, Hataji et al¹³ and Watz et al¹⁴ employed the duration

of PA and the mean intensity of PA as indices and both were improved by BD. Beeh et al¹⁵ reported that the duration of PA was improved, but the mean intensity of PA was not. O'Donnell et al¹⁶ employed only the mean intensity of PA as an index, and it was not improved by BD. Vorrink et al reported that the average percentage of PA for COPD patients vs controls was as follows: for intensity, 75%; for duration, 57%; and for PA counts, 56%,²⁹ which implies that the mean intensity of PA might be a less sensitive index than the duration of PA.

A positive effect of medication was observed in the duration of PA at relatively high intensities (≥ 3.0 METs and ≥ 3.5 METs), but not at low intensities. In the report of Hataji et al¹³ indacaterol improved the duration of PA at 2.9 METs or more but not at 2.3 METs or less. This is compatible with our results. Furthermore, our recent pilot study demonstrated that transdermal tulobuterol improved PA only at ≥ 3.5 METs in patients with COPD.³⁰ These results suggest that pharmacologic treatment could facilitate a relatively high intensity of PA.

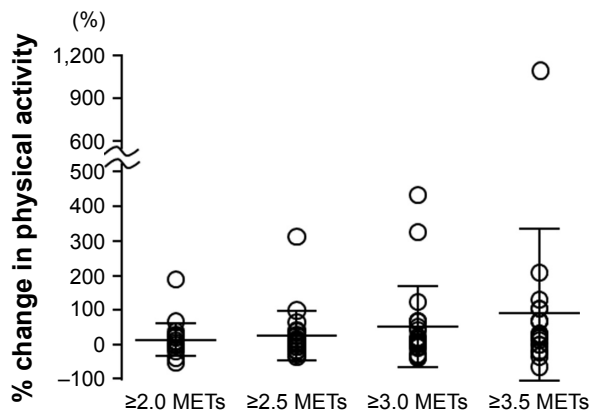


Figure 3 The degree of improvement in PA according to the intensity.
Notes: Horizontal lines indicate mean \pm SD. $P=0.193$ with one-way analysis of variance.
Abbreviations: PA, physical activity; SD, standard deviation; METs, metabolic equivalents.

Table 4 Correlation coefficients between % change in PA and baseline pulmonary function tests or ISWT

Variables	≥2.0 METs	≥2.5 METs	≥3.0 METs	≥3.5 METs	≥3.0 METs·hr
VC	0.094	0.326	0.418	0.237	0.352
FVC	0.094	0.334	0.473 ^a	0.228	0.407
FEV ₁	0.405	0.387	0.427	0.104	0.365
FRC	-0.247	0.068	0.008	-0.537 ^a	-0.052
RV	-0.396	-0.179	-0.384	-0.543 ^a	-0.425
TLC	-0.271	0.086	-0.085	-0.298	-0.162
IC/TLC	0.326	0.216	0.395	0.518 ^a	0.442
DLCO	0.381	0.147	0.352	0.262	0.382
ISWT	0.060	0.265	0.335	-0.065	0.233

Note: ^aP<0.05.

Abbreviations: PA, physical activity; ISWT, incremental shuttle walking test; METs, metabolic equivalents; METs·hr, METs multiplied by hours; VC, vital capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FRC, functional residual capacity; RV, residual volume; IC, inspiratory capacity; TLC, total lung capacity; DLCO, pulmonary carbon monoxide diffusing capacity.

The degree of the improvement in PA at ≥3.5 METs by medication was correlated with the baseline values of FRC, RV, and IC/TLC, suggesting that patients with better baseline pulmonary function might show greater improvements in their PA. Walker et al reported that the improvement in PA measured by a uniaxial accelerometer after 8-week rehabilitation was positively correlated with the baseline FEV₁,³¹ which was compatible with our results. The decline in FEV₁ was suppressed by BD more in stage II than in stage III or IV.³²⁻³⁴ BD might improve PA and pulmonary function in patients with better baseline pulmonary function.

Unexpectedly, the % change in the duration of PA by medication was not correlated with the % changes of any values of pulmonary function tests or ISWT. It has been reported that the increased PA was not correlated with the improved pulmonary function test score¹⁴ or increased exercise capacity.¹⁵ These reports are compatible with our results. The reason why they were not correlated is unclear, but one possibility is that the rapidity of improvement in PA might differ among parameters. Exercise capacity, quality of

life, and FEV₁ were improved by pulmonary rehabilitation at 3 months, while walking time was not improved at 3 months but was improved at 6 months in COPD patients.³⁵ In most of the studies about the efficacy of BD on PA, the efficacy was evaluated at 3 weeks or 4 weeks.^{13-16,30} The appearance of an adequate effect on PA might require more time than that on exercise capacity or pulmonary function. There was only one report with a 24-week placebo-control design in which the PA was not improved by tiotropium compared to placebo.¹⁸ In this report, however, the effects of seasonal differences, especially temperature, were not eliminated, and the baseline values of the duration of PA were largely different between the tiotropium group and placebo group.

Another possible reason for the non-correlation between % change in PA and those of pulmonary function tests or ISWT was that the improvement in PA by medication was derived not only from pulmonary function but also from other factors, including psychological or cardiovascular components. In some patients, medication might directly or indirectly influence factors other than pulmonary function.

Table 5 Correlation coefficients between % change in PA and % change in pulmonary function tests or ISWT

Variables	≥2.0 METs	≥2.5 METs	≥3.0 METs	≥3.5 METs	≥3.0 METs·hr
VC	-0.170	-0.102	-0.020	0.277	-0.003
IC	-0.130	0.118	0.071	-0.031	0.081
FVC	0.072	0.079	0.114	0.153	0.166
FEV ₁	-0.116	0.117	0.283	0.302	0.319
FRC	-0.296	-0.468 ^a	-0.374	0.065	-0.375
RV	0.062	-0.130	-0.209	0.059	-0.235
TLC	-0.238	-0.300	-0.304	0.101	-0.316
DLCO	-0.186	-0.309	-0.250	-0.298	-0.201
ISWT	-0.332	-0.401	-0.123	0.439	-0.059

Note: ^aP<0.05.

Abbreviations: PA, physical activity; ISWT, incremental shuttle walking test; METs, metabolic equivalents; METs·hr, METs multiplied by hours; VC, vital capacity; IC, inspiratory capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLCO, pulmonary carbon monoxide diffusing capacity.

There are several limitations that need to be addressed. First, the number of recruited patients was small. Though consideration of the conditions of data collection could provide us more reproducible results with a relatively smaller number of subjects, this study may not be conclusive. A larger study is required to clarify further the effect of pharmacologic treatment on PA in patients with COPD. Second, this study was a non-randomized and short-term study. A randomized study with a longer treatment duration considering seasonal effects should be performed. Third, the baseline and additional treatments were not fixed. As we aimed to evaluate the effect of pharmacologic treatment but not the effect of a specific BD, we recruited patients with no or one BD at baseline and added another BD according to the recommendation of the GOLD guideline.¹² Fourth, though the study subjects had not been diagnosed as having comorbidities, subclinical conditions, including cardiovascular dysfunction, depression, osteoporosis, or muscular weakness, were not completely excluded. The influence of comorbidities and muscular weakness on the PA in patients with COPD should be elucidated in future studies.

In conclusion, pharmacologic treatment could improve the duration of a relatively high intensity of PA in patients with COPD when medication was administered based on airflow limitation and breathlessness. The improvement in PA was correlated with the baseline pulmonary function but not with the improvement in pulmonary function test scores or exercise capacity.

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Author contributions

Y Minakata performed all procedures; Y Morishita set and analyzed the accelerometer; and T Ichikawa, K Akamatsu, T Hirano, M Nakanishi, K Matsunaga, and M Ichinose recruited subjects. All authors contributed to the writing of the manuscript and have approved the final version for submission. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest in this work.

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