

# Efficacy of tiotropium and indacaterol monotherapy and their combination on dynamic lung hyperinflation in COPD: a random open-label crossover study

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**Background and objective:** The difference in efficacy of long-acting muscarinic antagonists (LAMAs) and long-acting  $\beta_2$ -agonists (LABAs) for dynamic lung hyperinflation (DLH) in COPD is unclear. The purpose of this study was to elucidate the difference in efficacy of LAMA and LABA alone and the combination thereof for DLH.

**Subjects and methods:** Thirty stable patients were enrolled and randomly divided into two groups following baseline measurements. One group was treated with 5  $\mu$ g tiotropium (Respimat inhaler) for 4 weeks following a 4-week treatment with 150  $\mu$ g indacaterol, while the other group was treated with indacaterol for 4 weeks following a 4-week treatment with tiotropium. For both groups, these treatments were followed by a combination of the two drugs for 4 weeks. Pulmonary function tests, including DLH evaluated by metronome-paced incremental hyperventilation and exercise tolerance evaluated by the shuttle-walk test, were performed at the end of each treatment period.

**Results:** In total, 23 patients completed this study. Both tiotropium and indacaterol alone significantly increased forced expiratory volume in 1 second, exercise tolerance, and improved health status. Tiotropium significantly improved DLH, but indacaterol did not. The combination therapy resulted in further improvements in lung function and exercise tolerance, but not in DLH.

**Conclusion:** The efficacy of tiotropium in inhibiting DLH following metronome-paced incremental hyperventilation may be superior to that of 150  $\mu$ g indacaterol, although the effects on airflow obstruction were the same, and the combination therapy showed further improvement in airflow obstruction, but not in DLH.

**Keywords:** bronchodilator agents, clinical respiratory medicine, COPD, respiratory function tests, quality of life

## Introduction

Dynamic lung hyperinflation (DLH) is an important phenomenon that causes dyspnea and restricts exercise capacity in COPD.<sup>1,2</sup> It has been shown that improvements in dyspnea on effort following bronchodilator therapy correlate well with reductions in LH, as indicated by increases in inspiratory capacity (IC).<sup>3</sup> We have demonstrated that treatment with tiotropium for 2–3 months resulted in significant improvements in airflow obstruction, lung mechanics, oxygenation, and respiratory impedance in COPD, and it also significantly improved DLH following metronome-paced incremental hyperventilation (MPIH), exercise capacity, and health-related quality of life in emphysema-dominant COPD. However, treatment with salmeterol did not lead to any

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improvement in DLH.<sup>4</sup> It might be suggested that salmeterol does not improve DLH because of the weak bronchodilator action of salmeterol. However, indacaterol is close to a full agonist of the human  $\beta_2$ -adrenoceptor, whereas salmeterol displays only partial efficacy. Indacaterol has superior duration of action compatible with once-daily dosing in humans, as well as a fast onset of action, and it is called an ultralong-acting  $\beta_2$ -agonist.<sup>5</sup> Therefore, a different result for DLH will be obtained compared with results with tiotropium and indacaterol.

Current strategies recommend treatment with long-acting  $\beta_2$ -agonist (LABA)/long-acting muscarinic antagonist (LAMA) combination therapy for patients with moderate or more severe COPD.<sup>6</sup> Significant improvements in LH represented by IC, functional residual capacity (FRC), and residual volume (RV) were found following treatment with the once-daily tiotropium–olodaterol fixed-dose combination compared with placebo and monotherapies.<sup>7</sup> Moreover, the addition of indacaterol to tiotropium provided better effects on not only bronchodilation but also lung deflation (reflected by increased resting IC) compared with tiotropium monotherapy.<sup>8</sup> Berton et al<sup>9</sup> evaluated DLH via decrease in IC from preexercise levels during a constant-speed treadmill test to the limit of tolerance. Compared to formoterol monotherapy, the addition of tiotropium to formoterol further improved effort-induced DLH and exercise endurance in patients with moderate–severe COPD. However, little evidence of an additive effect of LABA with LAMA regarding DLH has been demonstrated. The purpose in this study was to determine the superiority of efficacy among the monotherapies of LAMA and LABA and the combination therapy of LAMA and LABA for DLH evaluated by MPIH.

## Subjects and methods

### Subjects

We recruited 30 symptomatic patients with stable COPD from the outpatient clinic of Shinshu University Hospital. COPD was diagnosed based on clinical history and symptoms and by pulmonary function characterized by irreversible airflow limitation in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy.<sup>6</sup> All subjects had smoking-related COPD without  $\alpha_1$ -antitrypsin deficiency, and had a smoking history of more than 30 pack-years. There were no current smokers. The patients who had any history of asthma or asthmatic symptoms, walking disability, severe arrhythmia, or heart failure, had suffered from respiratory tract infection or exacerbation of COPD during the preceding 3 months, and had been treated with oral

steroids and/or long-term oxygen therapy were excluded from the study. Severity of COPD, assessed according to GOLD strategy, was stage 1 (n=5), stage 2 (n=15), stage 3 (n=6), and stage 4 (n=4). For current therapies, 12 patients were being treated with LAMA, three with LAMA and LABA, four with inhaled corticosteroid (ICS) and LABA, one with LAMA and ICS, and six with LAMA and ICS/LABA. This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice and the Declaration of Helsinki, and was approved by the institutional research ethics committee of Shinshu University School of Medicine (2101). All patients gave written informed consent to participate. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000027446).

### Protocol

This was a random open-label crossover study. Subjects were divided into two groups at random for an accurate evaluation of the influence of the order of drug treatments with tiotropium and indacaterol. The random-allocation sequence was done using sequentially numbered containers. One group was treated with a 5  $\mu\text{g}$  once-daily dosage of tiotropium through a soft-mist inhaler (Respimat) for 4 weeks following a 4-week treatment with a 150  $\mu\text{g}$  once-daily dosage of indacaterol through a dry-powder inhaler, whereas the other group was treated with indacaterol for 4 weeks following a 4-week treatment with tiotropium in the same manner. Finally, both groups were treated with a combination of the two drugs (tiotropium + indacaterol) for 4 weeks. Health status was evaluated using the COPD-assessment test (CAT),<sup>10</sup> activity of daily life (ADL) was evaluated using the pulmonary emphysema activity of daily life (P-ADL),<sup>11</sup> and pulmonary function tests, including DLH evaluated by MPIH and exercise tolerance evaluated by shuttle-walk test, were performed at baseline and at the end of each treatment period. Pulmonary function tests were performed 2–3 hours after inhalation of the test drug. The primary end point was DLH following MPIH and IC at a rate of 30 or 40 breaths/min (bpm; IC<sub>30</sub> or IC<sub>40</sub>).

### Pulmonary function test

Spirometry, FRC lung volume, and lung-diffusion capacity for carbon monoxide (DL<sub>CO</sub>) were measured using a Chestac 8900 (Chest MI, Tokyo, Japan). FRC was measured using a body box, after which the subject immediately inspired to total lung capacity (TLC) and expired maximally to RV, allowing calculation of lung volume and RV/TLC. For predicted values for forced expiratory volume in 1 second

(FEV<sub>1</sub>) and vital capacity (VC), Japanese local reference data<sup>12</sup> developed by the Japanese Respiratory Society were adopted, and predicted values for DL<sub>CO</sub> and lung volumes (FRC, RV, and TLC) measured by body plethysmography were determined using the formulae of Nishida et al<sup>13</sup> and Boren et al,<sup>14</sup> respectively. Respiratory impedance was measured using a MostGraph 01 (Chest MI).

## Evaluation of DLH following MPIH

DLH was evaluated by MPIH with incremental increases from IC<sub>rest</sub> to IC<sub>20</sub>, IC<sub>30</sub>, and IC<sub>40</sub>, in accordance with our previous report.<sup>15</sup> IC and VC were measured immediately after breathing at a rate of 20 bpm paced by a metronome for 30 seconds following the measurement of IC and VC at rest. Consequently, the breathing rate was increased to 30 bpm and 40 bpm in 30-second increments, and IC and VC were again measured immediately after MPIH for 30 seconds at each breathing rate. DLH was evaluated by decreases in IC or percentage change from IC<sub>rest</sub> to IC<sub>20</sub> ( $\Delta IC_{20}$ ;  $IC_{20} - IC_{rest}$ ),  $\Delta IC_{30}$ , and  $\Delta IC_{40}$ .

## Statistical analysis

It was calculated that a sample size of 24 patients would have 80% power to detect a difference of 300 mL in mean IC<sub>30</sub> or IC<sub>40</sub>, the primary end point, following treatment, assuming an SD of 500 mL and two-sided significance level of 5%. Assuming a dropout rate of approximately 20%, it was calculated that a total of 30 patients would need to be randomized. Values in the text, figures, and tables represent mean  $\pm$  standard error of the mean. Repeated-measures analysis of variance was used to test for significant differences at different visits and time points according to each treatment. Comparisons of variables at baseline and at the end of each treatment were performed using paired *t*-tests. All statistical analyses were performed using Windows-compatible software (StatFlex version 6.0; Artech, Osaka, Japan). *P*<0.05 was considered significant for all statistical analyses.

## Results

Of the 30 registered patients, seven dropped out. One patient dropped out due to incongruity of the throat, one due to cough and exacerbation of dyspnea, and one due to dysuria when they switched to tiotropium. Three other patients dropped out due to exacerbation. One remaining patient refused clinical trial continuation. As a result, 23 patients completed the clinical trial. Table 1 shows the characteristics and data from the pulmonary function test for patients who completed the trial. There was no meaningful difference between the

**Table 1** Characteristics at baseline of 23 patients with COPD

Age, years	74.7 $\pm$ 1.5
Sex (male/female)	21/2
Smoking history, packs/year	55.4 $\pm$ 4.1
BMI, kg/m <sup>2</sup>	22.7 $\pm$ 0.5
CAT score	12 $\pm$ 1.5
P-ADL score	215 $\pm$ 2
VC, %	96.2 $\pm$ 5.7
IC, L	1.98 $\pm$ 0.12
FEV <sub>1</sub> , L	1.48 $\pm$ 0.12
FEV <sub>1</sub> , %	59.0 $\pm$ 4.8
GOLD stage (1/2/3/4)	3/13/4/3
FEV <sub>1</sub> /FVC, %	47.4 $\pm$ 3.2
FRC, %	125.4 $\pm$ 8.5
RV, %	181.3 $\pm$ 10.6
TLC, %	129.1 $\pm$ 4.6
RV/TLC, %	47.7 $\pm$ 2.1
R <sub>aw</sub>	2.3 $\pm$ 0.21
DL <sub>CO</sub> , %	69.7 $\pm$ 4.4

**Note:** Data expressed as mean  $\pm$  standard error of mean.

**Abbreviations:** BMI, body-mass index; CAT, COPD-assessment test; P-ADL, pulmonary emphysema activity of daily life; VC, vital capacity; IC, inhaled corticosteroid; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; R<sub>aw</sub>, airway resistance; DL<sub>CO</sub>, lung-diffusion capacity for carbon monoxide.

tiotropium-precedence group (n=11) and the indacaterol-precedence group (n=12) before the clinical trial started.

CAT scores decreased significantly following each monotherapy and further decreased following combination therapy (Table 2). A significant improvement was observed in P-ADL following combination therapy. FEV<sub>1</sub> increased significantly following treatment with each monotherapy, to the same level. The combination therapy showed a more significant increase in FEV<sub>1</sub>. There were no significant changes in lung volume following each treatment. Airway resistance showed significant improvements following tiotropium monotherapy and combination therapy. Among the data obtained from a MostGraph 01, resonant frequency and within-breath changes in reactance at 5 Hz frequency were significantly improved following combination therapy.

There were no significant changes in any DLH indices following indacaterol monotherapy. However, IC<sub>20</sub>, IC<sub>30</sub>, and IC<sub>40</sub> values following tiotropium monotherapy and IC<sub>30</sub> and IC<sub>40</sub> values following combination therapy increased significantly (Table 3, Figure 1). Furthermore, the decrease in IC from IC<sub>rest</sub> to IC<sub>40</sub> and  $\Delta IC_{40}$  was inhibited significantly by combination therapy (Figure 2). Table 4 shows the results of the shuttle-walk test. Significant differences were not observed in maximum Borg scale score, lowest peripheral oxygen saturation, maximum pulse rate, or blood pressure at the end of exercise load, but significant increases in walking

**Table 2** Results of questionnaires on health status and activity of daily life (ADL) and of the pulmonary function test

	Baseline	Tiotropium (Tio)	Indacaterol (Ind)	Tio + Ind
CAT score	12±1.5	9±1.5**	9.5±1.6*	7.4±1.2**
P-ADL score	214.8±2.1	214.5±0.15	215±2.3	217.0±1.7*#
VC, L	3.34±0.15	3.33±0.16	3.31±0.17	3.33±0.15
FVC, L	3.1±0.16	3.09±0.15	3.09±0.16	3.16±0.17
FEV <sub>1</sub> , L	1.48±0.12	1.55±0.12**	1.55±0.13*	1.63±0.14**§
FRC, L	4.2±0.23	4.18±0.27	4.06±0.25	4.05±0.23
RV, L	3.11±0.2	3.07±0.25	3.18±0.26	2.99±0.23
TLC, L	6.48±0.22	6.35±0.25	6.39±0.26	6.37±0.27
RV/TLC, %	47.7±2.1	47±2.2	47.2±2.2	46.1±2.1
R <sub>3w</sub> , cmH <sub>2</sub> O·L <sup>-1</sup> ·second	2.3±0.21	1.87±0.15**	2.05±0.22	1.68±0.15**#
Rrs <sub>5</sub> , cmH <sub>2</sub> O·L <sup>-1</sup> ·second	2.72±0.3	2.73±0.26	2.63±0.22	2.78±0.27
Rrs <sub>5</sub> -Rrs <sub>20</sub> , cmH <sub>2</sub> O·L <sup>-1</sup> ·second	0.74±0.11	0.66±0.08	0.67±0.09	0.71±0.11
Xrs <sub>5</sub> , cmH <sub>2</sub> O·L <sup>-1</sup> ·second	-1.57±0.3	-1.37±0.25	-1.33±0.3	-1.21±0.26
F <sub>res</sub> , Hz	15.5±1.4	14.3±1.2	13.4±1.3	12.6±1.4*
ΔXrs <sub>5</sub> , cmH <sub>2</sub> O·L <sup>-1</sup> ·second	-0.75±0.26	-0.7±0.26	-0.59±0.27	-0.06±0.3*#§§

**Notes:** Data expressed as mean ± standard error of mean. \*P<0.05, \*\*P<0.01 vs baseline; #P<0.05 vs Ind; §P<0.05, §§P<0.01 vs Tio.

**Abbreviations:** CAT, COPD-assessment test; P-ADL, pulmonary emphysema activity of daily life; VC, vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; R<sub>3w</sub>, airway resistance; Rrs<sub>5</sub>, respiratory resistance at 5 Hz; Rrs<sub>20</sub>, respiratory resistance at 20 Hz; RV, residual volume; TLC, total lung capacity; Xrs<sub>5</sub>, respiratory reactance at 5 Hz; F<sub>res</sub>, resonant frequency; ΔXrs<sub>5</sub>, within-breath changes in Xrs<sub>5</sub>.

distance were observed following each monotherapy and patients were able to walk the farthest following combination therapy.

## Discussion

In the present study, tiotropium improved DLH following hyperventilation, but indacaterol did not. In contrast, a similar effect on airflow obstruction was observed. Compared with each monotherapy, combination therapy may be more effective for health status, ADL, airflow obstruction, and exercise tolerance, but not for DLH following MPIH.

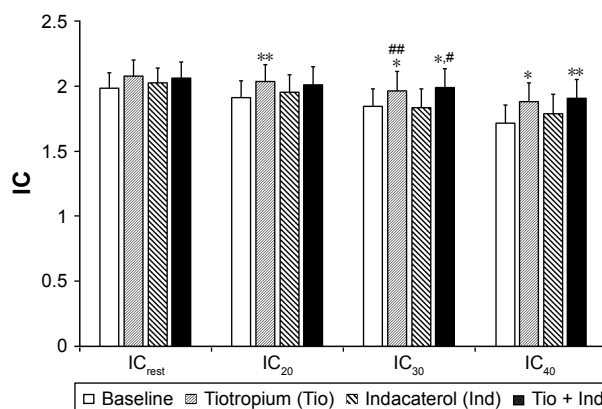
The recommended first-line treatment medicine for COPD has been a long-acting bronchodilator, and the efficacy of combination therapy using drugs with different action mechanisms should be determined. The combination therapy of LAMA and LABA for the improvement of pulmonary function has been shown to be superior to that of each monotherapy, and the combination results in an improvement in quality of life and exercise tolerance.<sup>16</sup> We have demonstrated that treatment with tiotropium showed a significant improvement in DLH following MPIH, as well as an improvement in pulmonary function and exercise capacity and health-related quality of life, in emphysema-dominant

**Table 3** Dynamic lung hyperinflation following incremental hyperventilation

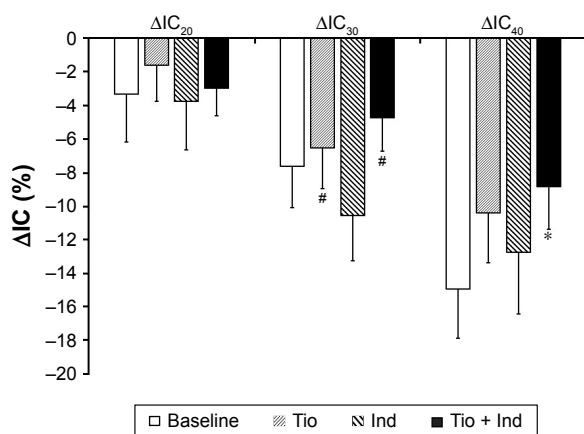
	Baseline	Tiotropium (Tio)	Indacaterol (Ind)	Tio + Ind
IC <sub>rest</sub> , L	1.98±0.12	2.08±0.12	2.02±0.12	2.06±0.13
IC <sub>20</sub> , L	1.91±0.13	2.04±0.13**	1.95±0.13	2.01±0.14
IC <sub>30</sub> , L	1.84±0.13	1.96±0.15*##	1.84±0.14	1.99±0.15*#
IC <sub>40</sub> , L	1.71±0.14	1.88±0.14*	1.79±0.15	1.9±0.15**
-IC <sub>20</sub> , L	-0.07±0.06	-0.04±0.04	-0.07±0.06	-0.05±0.04
-IC <sub>30</sub> , L	-0.14±0.05	-0.11±0.05	-0.19±0.06	-0.07±0.04#
-IC <sub>40</sub> , L	-0.27±0.06	-0.20±0.06	-0.23±0.08	-0.16±0.05*
ΔIC <sub>20</sub> , %	-3.3±2.9	-1.6±2.2	-3.8±2.9	-3±1.6
ΔIC <sub>30</sub> , %	-7.6±2.4	-6.5±2.4#	-10.5±2.7	-4.7±2#
ΔIC <sub>40</sub> , %	-14.9±3	-10.4±3	-12.7±3.7	-8.8±2.6*

**Notes:** Data expressed as mean ± standard error of mean. \*P<0.05, \*\*P<0.01 vs baseline; #P<0.05, ##P<0.01 vs Ind.

**Abbreviations:** IC, inspiratory capacity; IC<sub>rest</sub>, resting IC; IC<sub>20</sub>, IC at 20 breaths/min; -IC<sub>20</sub>, decrease in IC from IC<sub>rest</sub> to IC<sub>20</sub>; ΔIC<sub>20</sub>, change in IC from IC<sub>rest</sub> to IC<sub>20</sub>; IC<sub>30</sub>, IC at 30 breaths/min; -IC<sub>30</sub>, decrease in IC from IC<sub>rest</sub> to IC<sub>30</sub>; ΔIC<sub>30</sub>, change in IC from IC<sub>rest</sub> to IC<sub>30</sub>; IC<sub>40</sub>, IC at 40 breaths/min; -IC<sub>40</sub>, decrease in IC from IC<sub>rest</sub> to IC<sub>40</sub>; ΔIC<sub>40</sub>, change in IC from IC<sub>rest</sub> to IC<sub>40</sub>.

**Figure 1** Effects of tiotropium (Tio) and indacaterol (Ind) alone and the combination thereof.

**Notes:** Effect on inspiratory capacity (IC) at rest (IC<sub>rest</sub>) and IC following metronome-paced incremental hyperventilation at rates of 20, 30, and 40 breaths/min (IC<sub>20</sub>, IC<sub>30</sub>, and IC<sub>40</sub>, respectively). Data expressed as mean ± standard error of mean. \*P<0.05, \*\*P<0.01 vs baseline; #P<0.05, ##P<0.01 vs Ind.



**Figure 2** Effects of tiotropium (Tio) and indacaterol (Ind) alone and the combination of thereof.

**Notes:** Effect on changes in IC following metronome-paced incremental hyper-ventilation at rates of 20, 30, and 40 breaths/min (%Ch.  $\Delta IC_{20}$ ,  $IC_{20}$ , and  $IC_{40}$ , respectively) from IC at rest. Data expressed as mean  $\pm$  standard error of mean. \* $P < 0.05$  vs baseline, # $P < 0.05$  vs Ind.

**Abbreviations:** IC, inspiratory capacity;  $IC_{rest}$ , resting IC;  $IC_{20}$ , IC at 20 breaths/min;  $\Delta IC_{20}$ , change in IC from  $IC_{rest}$  to  $IC_{20}$ ;  $IC_{30}$ , IC at 30 breaths/min;  $\Delta IC_{30}$ , change in IC from  $IC_{rest}$  to  $IC_{30}$ ;  $IC_{40}$ , IC at 40 breaths/min;  $\Delta IC_{40}$ , change in IC from  $IC_{rest}$  to  $IC_{40}$ .

COPD, but the treatment with salmeterol did not show any improvement in DLH.<sup>4</sup> We have suggested that the difference in the efficacy for DLH following MPIH may be due to the weak action of the  $\beta_2$ -agonist. In this study, the efficacy of an ultralong-acting  $\beta_2$ -agonist with more effective action for bronchodilation, indacaterol, was examined. Although indacaterol treatment significantly improved airflow obstruction and exercise tolerance to the same extent as tiotropium, indacaterol could not inhibit DLH following MPIH.

It has been recommended based on consistent evidence that treatment with tiotropium can reduce DLH during or immediately after exercise.<sup>17</sup> We also demonstrated that tiotropium significantly reduced DLH following MPIH in the present study, similar to our previously reported result.<sup>4</sup> The additive effects of tiotropium with formoterol on effort-related DLH and exercise endurance in patients with moderate-severe COPD were also demonstrated,<sup>9</sup> and the advantageous effects were more likely to be found in patients who were

severely disabled and functionally responsive to the addition of the cholinergic blockade. However, for the  $\beta_2$ -agonist, we demonstrated that treatment with both a short-acting muscarinic antagonist and a short-acting  $\beta_2$ -agonist (SABA) significantly increased IC following MPIH. Furthermore, SABA significantly inhibited the decrease in IC following hyperventilation.<sup>18</sup> Moreover, the addition of SABA to current therapy, including LAMA, resulted in further improvement in DLH following MPIH, with an improvement in the exercise capacity of patients with moderate-very severe COPD who showed dyspnea on effort despite their current therapy.<sup>15</sup> Beeh et al<sup>19</sup> examined the effect of 300  $\mu$ g inhaled once-daily indacaterol on peak and “isotime” exercise IC in patients with COPD in a randomized, double-blind, placebo-controlled, two-period crossover study. Indacaterol showed statistically significant improvements over placebo in peak and isotime IC, along with improvements in resting IC, trough  $FEV_1$ , dyspnea, and exercise-endurance time. The results in the present study were different from those reported by Beeh et al.<sup>19</sup> One possible reason for the difference may have been the difference in method of evaluating DLH from previous reports, which may have led to conflicting results. A second reason may be the different dose used in our study. Beeh et al used inhaled 300  $\mu$ g once-daily indacaterol, but we used only half this dose and thus did not obtain a sufficient inhibitory effect on DLH. In our country, 150  $\mu$ g once-daily inhaled indacaterol is approved and is the upper-limit dose. The severity of the COPD of the patients enrolled in the present study was almost the same as that in the report by Beeh et al. In their study, IC at rest and trough  $FEV_1$  increased by 182 mL and 145 mL, respectively, on average. However, in the present study, IC at rest and  $FEV_1$  increased by only 40 mL and 70 mL, respectively, on average, possibly suggesting that efficacy was insufficient. Kato et al compared the efficacy of inhaled indacaterol at doses of 150  $\mu$ g, 300  $\mu$ g, and 600  $\mu$ g. Inhalation of 150  $\mu$ g indacaterol caused a significant improvement; however, at the dose of 300  $\mu$ g, trough  $FEV_1$  was further increased and reached its peak.<sup>20</sup> In addition, the

**Table 4** Exercise tolerance evaluated by shuttle-walk test

	Baseline	Tiotropium (Tio)	Indacaterol (Ind)	Tio + Ind
BS <sub>max</sub> score	4.6 $\pm$ 0.5	5.1 $\pm$ 0.4	4.9 $\pm$ 0.3	5.2 $\pm$ 0.4
Lowest SpO <sub>2</sub> , %	89.5 $\pm$ 0.3	88.5 $\pm$ 1.6	89.2 $\pm$ 1.5	89.6 $\pm$ 1.3
PR <sub>max</sub> , beats/min	111.6 $\pm$ 3.6	111.0 $\pm$ 4.4	111.8 $\pm$ 3.4	109.8 $\pm$ 3.8
Systolic BP <sub>max</sub> , mmHg	158.1 $\pm$ 5.4	154.5 $\pm$ 4.5	157.2 $\pm$ 4.4	153.1 $\pm$ 4.5
Diastolic BP <sub>max</sub> , mmHg	82.3 $\pm$ 3.5	84.1 $\pm$ 4.5	84.3 $\pm$ 4.1	79.3 $\pm$ 3.1
Walking distance, m	384.8 $\pm$ 34.5	425.2 $\pm$ 29.2*	430.0 $\pm$ 35.6**	447.4 $\pm$ 37.7**

**Notes:** Data expressed as mean  $\pm$  standard error of mean. \* $P < 0.05$ , \*\* $P < 0.01$  vs baseline.

**Abbreviations:** BS<sub>max</sub>, Borg scale (modified) maximum; SpO<sub>2</sub>, peripheral oxygen saturation; PR<sub>max</sub>, maximum pulse rate; BP<sub>max</sub>, maximum blood pressure.

efficacy of bronchodilation for Japanese individuals has been demonstrated to be equal to Caucasians. The combination therapy resulted in an additive effect on bronchodilation; however, no additive effects were observed on DLH following hyperventilation. These findings may suggest that the lack of efficacy regarding DLH may not be a problem solely due to the dose of indacaterol. It has been demonstrated that LAMA may be superior to LABA<sup>21</sup> when comparing the effects of LAMA and LABA monotherapy on the exacerbation of COPD. One large difference in action mechanism is the inhibitive effect on mucous production due to differences between LAMA and LABA in their anticholinergic action. Therefore, treatment with tiotropium might reduce mucous hypersecretion at the site of peripheral airways. It may possibly contribute to improvements in air trapping and DLH.

This study is subject to some limitations. The first limitation concerns sample size. Prior to the study, sample size was calculated, and a total of 30 patients needed to be randomized. However, the SDs of IC<sub>30</sub> and IC<sub>40</sub> at baseline were slightly greater than those predicted and more than 20% of participants dropped out, resulting in a decrease in power to detect a difference. The small sample size of each group and the wide distribution of severity might have affected the results. The second limitation concerns the respiratory rate. With regard to the rate of respiration following hyperventilation, Gelb et al<sup>22</sup> reported that in patients with moderate–severe COPD, metronome-timed 20-second hyperventilation at twice the respiratory rate of that at rest reduced IC and was useful in dynamic hyperinflation screening. We evaluated IC at three respiratory rates: 20, 30, and 40 bpm. However, we did not determine the extent of the increase in respiratory rate during exercise. The third limitation concerns the absence of a comparison of our quantitative evaluation following hyperventilation and the conventional evaluation of dynamic hyperinflation during or immediately after exercise loading. This remains to be investigated in the future.

In conclusion, 5 µg once-daily inhaled tiotropium improves DLH following hyperventilation, but 150 µg inhaled once-daily indacaterol does not, although they have a similar effect on airflow obstruction. Additionally, combination therapy may be more effective for health status, ADL, airflow obstruction, and exercise tolerance than each monotherapy, but it is not more effective for DLH following hyperventilation. These findings may be attributed to the insufficient effect of low-dose indacaterol.

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## Disclosure

The authors report no conflicts of interest in this work.

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