# Additive efficacy of short-acting bronchodilators on dynamic hyperinflation and exercise tolerance in stable COPD patients treated with long-acting bronchodilators

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Abstract

Summary

The purpose of this study was to clarify the additive efficacy of short-acting $\beta_2$-agonists (SABA) or muscarinic antagonists (SAMA) on dynamic hyperinflation and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) who had been treated with long-acting bronchodilators.

Thirty-two patients with stable COPD who had been treated with long-acting bronchodilators, including long-acting muscarinic antagonists (LAMA), were examined by pulmonary function tests, dynamic hyperinflation evaluated by the method of step-wise metronome-paced incremental hyperventilation, and the incremental shuttle walking test before and after inhalation of SABA or SAMA. The additive efficacy of the two drugs was analyzed.

Inhalation of SABA and SAMA improved airflow limitation and dynamic hyperinflation in stable COPD patients who had been treated with LAMA. Inhalation of SABA decreased respiratory resistance and the difference in respiratory resistance at 5 Hz and 20 Hz. On the whole, the additive efficacy of SABA on airflow limitation and dynamic hyperinflation was superior to that of SAMA. Furthermore, inhalation of SABA resulted in relief of breathlessness

during exercise and significant improvement in exercise capacity.

Inhalation of SABA resulted in significant improvement in exercise tolerance, which may have been due to improvement in dynamic hyperinflation. Single use of SABA before exercise, in addition to regular treatment with LAMA, may therefore be useful in stable COPD patients.

## Introduction

Dynamic hyperinflation is attributed to air trapping during exercise, caused by a decrease in elastic recoil pressure due to destruction of the alveoli and narrowing of the small airways in patients with chronic obstructive pulmonary disease (COPD).[1,2] There is a significant relationship between dynamic hyperinflation and exertional dyspnea or decreased exercise tolerance in COPD patients,[1,3,4] thus suggesting that dynamic hyperinflation importantly contributes to exertional dyspnea and impairment of exercise tolerance in COPD.

According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines,[5] bronchodilator medications play a central role in the management of stable COPD. The types of bronchodilators most commonly used are $\beta_2$-agonists and anticholinergic agents. Of all the bronchodilators, the long-acting muscarinic antagonists (LAMA) are the most effective agents for COPD when used alone. However, COPD patients still have exertional dyspnea in their daily lives despite treatment with long-acting bronchodilators. Short-acting $\beta_2$-agonists (SABA) and muscarinic antagonists (SAMA) are recommended to use for relief of dyspnea as-needed in combination with regular use of long-acting bronchodilators.[5]

We have developed the method to evaluate dynamic hyperinflation by the metronome-paced incremental hyperventilation (MPIH) technique, and demonstrated that both SABA and SAMA are effective for reducing dynamic hyperinflation in COPD.[6] We also demonstrated that the treatment with tiotropium (LAMA) for eight weeks partially reduced dynamic hyperinflation following the incremental hyperventilation and improved exercise capacity and health-related quality of life in COPD.[7]

We hypothesized that the efficacy of SABA or SAMA on improving exercise capacity may be due to the relief of dynamic hyperinflation in stable COPD patients, and that it may also be additive to the efficacy of regular treatment with long-acting bronchodilators, including LAMA.

## Methods

### Subjects

Thirty-two stable COPD patients, with $FEV_1$/FVC <70% and $FEV_1$ values less than 80% of the predicted value after inhalation of a $\beta_2$-agonist (moderate-to-very severe COPD), were recruited from the outpatient clinic of Shinshu University Hospital from February 2007 to July 2009. COPD was diagnosed based on clinical history and symptoms, and pulmonary function characterized by irreversible airflow limitation in accordance with the GOLD guidelines.[5] All subjects had smoking-related COPD without α1-antitrypsin deficiency, and had a smoking history of more than 30 pack-years. Patients with any history of asthma or asthmatic symptoms as well as patients who had walking disability, severe arrhythmia or heart failure, or had suffered from respiratory tract infection or exacerbation of COPD during the preceding three months were excluded from the study. All subjects had been treated with tiotropium (18 μg, LAMA) once daily for more than three months, while continuing their other current therapy without any changes in dose. The subjects were randomized into two groups: **(1)** SABA group (n=16) or **(2)** SAMA group (n=16) as stated in the study protocol. The severity of COPD, assessed

according to the GOLD guidelines, was stage 2 (n=7), stage 3 (n=6) and stage 4 (n=3) in the SABA group, and was stage 2 (n=3), stage 3 (n=11) and stage 4 (n=2) in the SAMA group. There were no significant differences in the severity of COPD between the two groups. As the other current therapies being used in addition to tiotropium, 8 patients were being treated with long-acting $\beta_2$-agonists (LABA), 6 with inhaled corticosteroid (ICS) and 5 with oral theophylline in the SABA group, and 9 patients were being treated with LABA, 7 with ICS and 8 with oral theophylline in the SAMA group. The study was approved by the institutional research ethics committee of Shinshu University School of Medicine, and all patients gave written informed consent to participate.

Protocol

All patients received treatment with tiotropium in the morning on the day that the pulmonary function tests were performed, but did not use SABA or SAMA. Pulmonary function tests including respiratory impedance evaluated using an impulse oscillation system (IOS), dynamic hyperinflation following MPIH, and exercise capacity evaluated by the incremental shuttle walking test were performed. After completion of the baseline measurements, the subjects were

then enrolled in a randomized, open-label, comparative trial to evaluate the additive efficacy of SABA and SAMA. One group inhaled 20 μg of procaterol hydrochloride (SABA; Meptin®; Otsuka Pharmaceutical, Tokushima, Japan), while the other group inhaled 0.2 mg of oxitropium bromide (SAMA; Tersigan®; Boehringer Ingelheim, Ingelheim, Germany), using a metered-dose inhaler with a spacer device. Measurements were again performed 30 min after inhalation of procaterol hydrochloride or 60 min after inhalation of oxitropium bromide.

Pulmonary function tests

Spirometry and DLCO were measured using the Chestac-8800 (Chest Co Ltd, Tokyo, Japan). Functional residual capacity was measured using a Body Box (Medgraphic, Ann Arbor, MI), after which the subject immediately inspired to total lung capacity and expired maximally to residual volume, allowing calculation of lung volume and residual volume/total lung capacity. Local Japanese reference data,[8] developed by the Japanese Respiratory Society, were used to derive predicted values for $FEV_1$ and vital capacity, and predicted values for DLCO and lung volumes (functional residual capacity, residual volume, and total lung capacity) measured by body plethysmography were determined

using the formulas described by Nishida et al [9] and Boren et al [10], respectively.

Respiratory impedance was measured using an IOS (Masterscreen IOS; Erich Jaeger, Hoechberg, Germany), as described previously.[11,12] Respiratory impedance (Zrs) is characterized by two components: respiratory resistance (Rrs) and reactance (Xrs). Xrs undergoes a transition from negative to positive values as frequency ($f$) increases. The resonant frequency ($f$res) was determined as the frequency at which Xrs crossed zero and the elastic and inertial forces were equal in magnitude and opposite. Rrs and Xrs at lower oscillation frequencies and Rrs at higher frequencies were evaluated at oscillation frequencies of 5 Hz (Rrs5 and Xrs5) and 20 Hz (Rrs20). We also measured mean values of Rrs5 and Xrs5 in separated inspiration and expiration of tidal breath, and evaluated the difference between mean expiratory and inspiratory resistance (ΔRrs5) and reactance (ΔXrs5).

Evaluation of dynamic hyperinflation following MPIH

Dynamic hyperinflation was evaluated by metronome-paced hyperventilation, incrementally increasing the respiratory rate to 20, 30 and 40 breaths/min according to our previous reports.[6,7] End-expiratory lung volume (EELV) by body

plethysmography, inspiratory capacity (IC), and VC were measured immediately after breathing at resting respiratory rate for 30 s. Consequently, respiratory rate was increased to 20, 30 and 40 breaths/min in 30-s increments, and EELV, IC and VC were again measured immediately after metronome-paced hyperventilation for 30 s at each respiratory rate. Inspiratory capacity at resting respiratory rate was expressed as $IC_{at\ rest}$. Inspiratory capacity at rates of 20, 30, and 40 breaths per minute were expressed as $IC_{20}$, $IC_{30}$, and $IC_{40}$, respectively. Dynamic hyperinflation was evaluated by the decreases in inspiratory capacity from $IC_{at\ rest}$ to $IC_{20}$ ($IC_{rest\text{-}20}$; $IC_{20}$–$IC_{at\ rest}$), from $IC_{at\ rest}$ to $IC_{30}$ ($IC_{rest\text{-}30}$; $IC_{30}$–$IC_{at\ rest}$) and from $IC_{at\ rest}$ to $IC_{40}$ ($IC_{rest\text{-}40}$; $IC_{40}$–$IC_{at\ rest}$).

Incremental shuttle walking test

The incremental shuttle walking test (ISWT) was conducted using the protocol described by Singh et al.[13] Briefly, patients were required to walk around a 10-meter course with the walking speed of each 10-meter shuttle dictated by an audio signal played on a compact disk. The test commenced at an initial speed of 0.5 meters per second, with one-minute increments of 0.17 meter per second. The test was terminated when the patients were too breathless to

continue or failed to maintain the required speed on two consecutive shuttles. At the end of the test, patients rated their intensity of breathlessness by using a Borg 0-10 scale.[14] Oxygen saturation (PULSOX M2, Minolta Co. Ltd, Japan), heart rate, and blood pressure were measured prior to and at the termination of the test.

Data analysis

The values shown in the text, figures and tables represent means ± standard error of the mean (SEM). The data distribution of the variables in the two groups was first assessed with Bartlett's test. Data for the variables that showed a normal distribution were compared using the parametric Student's *t*-test. Data for the variables that did not show a normal distribution were compared using the nonparametric Mann-Whitney's *U*-test. The data distribution of the variables at baseline and after the inhalation of SABA or SAMA was first assessed with Bartlett's test. Data for the variables that showed a normal distribution were compared using the parametric paired *t*-test. Data for the variables that did not show a normal distribution were compared using the nonparametric Wilcoxon signed-rank test. Simple correlations between variables were examined by

calculating Pearson's product correlation coefficient. All statistical analyses were performed using a Windows-compatible software (Stat Flex version 5.0; Artech, Osaka, Japan). A value of $P<0.05$ was considered to be significant for the results of all statistical analyses.

## Results

### Clinical characteristics and pulmonary function tests

The characteristics and pulmonary function at baseline in the two groups are shown in **Table 1**. There were no significant differences in age, gender or body mass index between the two groups. There were no significant differences in VC, IC, $FEV_1$, $FEV_1$/FVC, RV, TLC, RV/TLC and DLCO between the two groups. $FEV_1$ was significantly increased compared to the baseline in both groups **(Table 2)**. However, there was a significant difference between the increase in $FEV_1$ in the SABA group and that in the SAMA group (0.14±0.02L vs. 0.08±0.02L, $p<0.05$). Rrs5, Rrs5-Rrs20 and $f$res were significantly decreased in the SABA group **(Table 2)**. In contrast, there were no significant changes following inhalation of SAMA in these parameters of respiratory impedance.

### Dynamic hyperinflation following MPIH

Inspiratory capacity was incrementally decreased as respiratory rate was incrementally increased in all patients before inhalation of SABA or SAMA. $IC_{20}$, $IC_{30}$ and $IC_{40}$ significantly increased, and $IC_{rest\text{-}30}$ and $IC_{rest\text{-}40}$ significantly decreased in the SABA group **(Figures 1 and 2)**. $IC_{40}$ significantly increased,

and $IC_{rest\text{-}40}$ significantly decreased in the SAMA group. These findings suggest that the additive efficacy of SABA on dynamic hyperinflation was superior to that of SAMA.

Incremental shuttle walking test

Walking distance of the ISWT was significantly increased following inhalation of SABA, but not following inhalation of SAMA **(Table 3)**. Maximum Borg scale for breathlessness after walking (BSmax) was significantly increased following inhalation of SAMA, suggesting that inhalation of SAMA did not result in relief of breathlessness during exercise. In contrast, BSmax remained unchanged following inhalation of SABA, suggesting that inhalation of SABA resulted in relief of breathlessness during exercise. There were no significant changes in maximum pulse rate and lowest $SpO_2$ during exercise after the drug inhalation in either of the groups. There was a significant correlation between the increases in walking distance of the ISWT and the increases in $IC_{40}$ following inhalation of SABA ($r=0.51$, $p<0.05$). In contrast, there was no significant correlation between the increases in walking distance of the ISWT and the increases in $FEV_1$ following inhalation of SABA.

## Discussion

Inhalation of SABA and SAMA improved airflow limitation and dynamic hyperinflation in stable COPD patients who had been treated with LAMA. Inhalation of SABA decreased respiratory resistance and the difference in respiratory resistance at 5 Hz and 20 Hz. Furthermore, inhalation of SABA resulted in relief of breathlessness during exercise and significant improvement in exercise capacity. On the whole, the additive efficacy of SABA on airflow limitation, dynamic hyperinflation and exercise tolerance was superior to that of SAMA. The increases in $IC_{40}$, but not the increases in $FEV_1$, had a significant correlation with the improvement in exercise capacity following inhalation of SABA, thus suggesting that significant improvement in exercise capacity may be due to improvement in dynamic hyperinflation.

We previously demonstrated that both SABA and SAMA are effective for reducing dynamic hyperinflation following MPIH, and that SABA is more effective than SAMA in COPD patients.[6] Previous studies have demonstrated that SABA is more effective for resting pulmonary function parameters than SAMA in stable COPD patients with a regular treatment with LAMA.[15,16] In this study, the additive efficacy of SABA on airflow limitation, dynamic hyperinflation and exercise

tolerance was superior to that of SAMA in stable COPD patients treated with LAMA. These findings suggest that SABA is better to use for relief of dyspnea as-needed in stable COPD patients regardless of regular treatment with LAMA.

Sukisaki et al. demonstrated that inhalation of procaterol hydrochloride (SABA) enhances the effect of exercise training in the absence of any change in $FEV_1$ during rehabilitation of COPD patients, and the effect lasted for at least four hours after inhalation.[17] They also demonstrated that the mean walking distance of the ISWT was significantly increased by 37 m following inhalation of SABA in 19 patients with moderate-to-severe COPD. In this study, it was significantly increased by 19.4 m following inhalation of SABA, which was smaller than the increase they demonstrated, and did not reach a statistically significant increase in the ISWT (>40 m) [18] and the minimum clinically important improvement for the ISWT (>47.5 m) [19]. The reason for the difference between the studies may be because we investigated the additive efficacy of SABA in stable COPD patients who had been treated with LAMA, and because very severe COPD patients were included in this study.

BSmax of the ISWT remained unchanged following inhalation of SABA, probably due to the fact that it was obtained at peak load during exercise, and

walking distance also significantly increased. If Borg scale score would be obtained at the same load or at the same time during exercise, it is thus speculated that Borg scale score would decrease following inhalation of SABA.

Patients with COPD frequently report dyspnea related to everyday tasks.[20,21] They often decrease their physical activity because exercise can worsen dyspnea. As a consequence, they tend to have problems including exercise deconditioning, relative social isolation, altered mood states, especially depression, muscle wasting, weight loss and osteoporosis.[5,22] The progressive deconditioning associated with inactivity initiates a vicious cycle, with dyspnea becoming problematic at ever lower physical demands.[5] To address these problems, it is important to improve dyspnea in daily life leading to decreased physical activity. Therefore, it is noteworthy to pay attention to the additive efficacy of SABA for stable COPD patients together with pulmonary rehabilitation. Single use of SABA before exercise, in addition to regular treatment with LAMA, may therefore be useful in stable COPD patients

COPD increases the risk of cardiovascular disease by two- to threefold [23-20] by itself. Furthermore, stimulation of $\beta_2$-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm

disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy.[5] Hypokalemia occurs with $\beta_2$-adrenergic stimulation as a result of intracellular shifts of potassium into skeletal muscle,[24] and has been associated with an increased risk for ventricular tachycardia and fibrillation in susceptible patients.[25] Elevated heart rate has been shown to be a strong independent risk factor for the development of cardiomyopathy, coronary artery disease, fatal myocardial infarction, sudden death, cardiovascular mortality, and total mortality.[26] In this study, there were no significant changes in maximum pulse rate and lowest $SpO_2$ during exercise following the drug inhalation in either group. However, it should be noted that SABA occasionally has some adverse effects, particularly in patients with underlying ischemia, myocardial infarction, arrhythmia, or congestive heart failure.

The possible effects of tachyphylaxis of short-acting bronchodilators can be problematic in clinical practice. However, previous studies have demonstrated the effectiveness of long-term regular bronchodilator therapy with procaterol hydrochroride [27] and oxirtopium bromide [28] in stable COPD patients.

One limitation of this study is that the severity of COPD, assessed according

to the GOLD guidelines, tended to be higher in the SAMA group and this may have influenced the results. However, there were no significant differences in severity of COPD and the results at baseline between the groups. Another limitation of the study was the relatively small sample size, and further larger studies are required to confirm these results.

In conclusion, inhalation of SABA and SAMA improved airflow limitation and dynamic hyperinflation in patients with moderate-to-very severe COPD who had been treated with LAMA. The additive efficacy of SABA was superior to that of SAMA. Furthermore, inhalation of SABA resulted in significant improvement in exercise capacity, which may have been due to improvement in dynamic hyperinflation. Single use of SABA before exercise, in addition to regular treatment with LAMA, may therefore be useful in stable COPD patients.

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Disclosure

The authors report no conflicts of interest in this work.

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Legends

**Figure 1. Effects of SABA or SAMA on dynamic hyperinflation following metronome-paced incremental hyperventilation. Inspiratory capacity at resting respiratory rate, and the rate of 20, 30 and 40 breath per minute before and after inhalation of SABA or SAMA are shown.**

Values are means ± standard error of the mean. *p<0.05 and **p<0.01 vs. pre inhalation

SABA, short-acting $\beta_2$ agonist; SAMA, short-acting muscarinic antagonist; IC at rest, inspiratory capacity at resting respiratory rate; $IC_{20}$, $IC_{30}$, and $IC_{40}$, inspiratory capacity at the rate of 20, 30 and 40 breaths per minute, respectively

**Figure 2. Effects of SABA or SAMA on dynamic hyperinflation following metronome-paced incremental hyperventilation. Decreases in inspiratory capacity from resting respiratory rates to the rate of 20, 30, and 40 breath per minute before and after inhalation of SABA or SAMA are shown.**

Values are means ± standard error of the mean. *p<0.05 and **p<0.01 vs. pre inhalation

SABA, short-acting $\beta_2$ agonist; SAMA, short-acting muscarinic antagonist; $IC_{rest\text{-}20}$, $IC_{rest\text{-}30}$ and $IC_{rest\text{-}40}$, decreases in IC from $IC_{at\ rest}$ to $IC_{20}$ ($IC_{20}$–$IC_{at\ rest}$),

from $IC_{at\ rest}$ to $IC_{30}$ ($IC_{30}$–$IC_{at\ rest}$) and from $IC_{at\ rest}$ to $IC_{40}$ ($IC_{40}$–$IC_{at\ rest}$), respectively

**Table 1. Baseline characteristics of the SABA and SAMA groups**

Values are means ± standard error of the mean.

SABA, short-acting $\beta_2$ agonist; SAMA, short-acting muscarinic antagonist; VC, vital capacity; IC, inspiratory capacity; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide; pred., predicted

**Table 2. Effects of SABA or SAMA on $FEV_1$ and respiratory impedance**

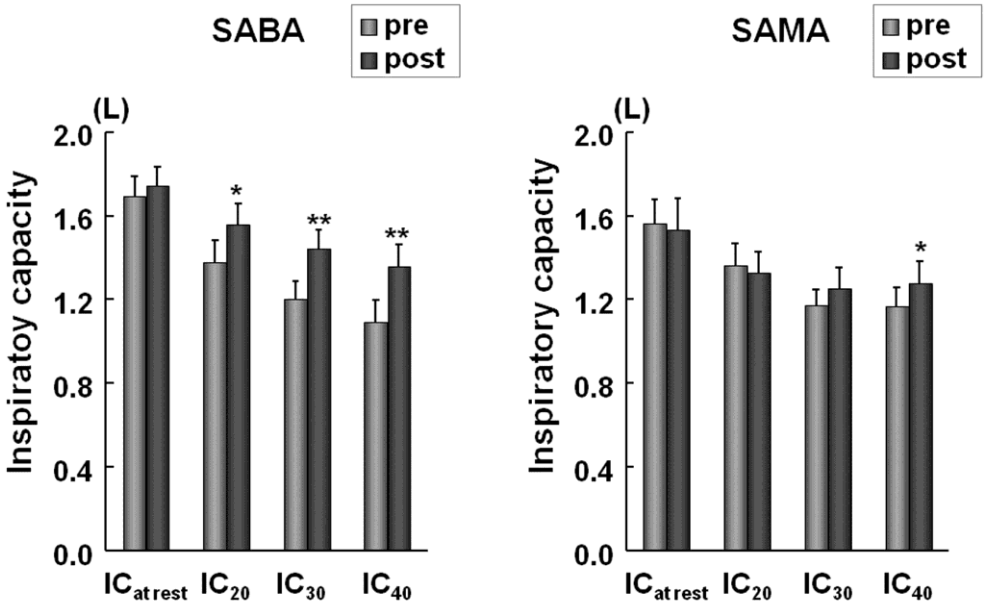
Values are means ± standard error of the mean. *p<0.05 and **p<0.01 vs. pre inhalation

SABA, short-acting $\beta_2$ agonist; SABA, short-acting muscarinic antagonist; $FEV_1$, forced expiratory volume in 1 second; Rrs5 and Rrs20, respiratory resistances at 5 Hz and 20 Hz frequencies; Xrs5, respiratory reactance at 5 Hz frequencies; ΔRrs5, within-breath changes in Rrs5; ΔXrs5, within-breath changes in Xrs5; $f$res, resonant frequency

**Table 3. Effects of SABA or SAMA on the incremental shuttle walking test**

Values are means ± standard error of the mean. *p<0.05 and **p<0.01 vs. pre inhalation

SABA, short-acting $\beta_2$ agonist; SAMA, short-acting muscarinic antagonist; PRmax, maximum pulse rate; BSmax, maximum Borg scale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IC at rest
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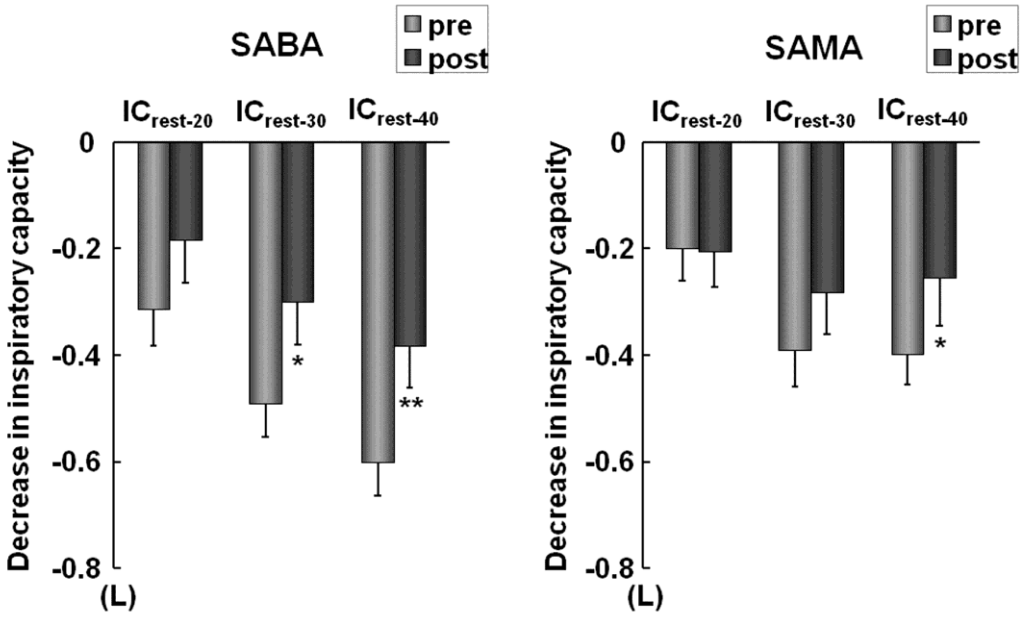
Figure 1.


SABA
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SAMA
pre
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IC rest-20
IC rest-30
IC rest-40
Decrease in inspiratory capacity
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-0.2
-0.4
-0.6
-0.8
(L)
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Figure 2.

Table 1. Baseline characteristics of the SABA and SAMA groups

| | SABA (n=16) | SAMA (n=16) |
|---|---|---|
| Gender, male/female | 15/1 | 16/0 |
| Age, yr | 73±2 | 76±2 |
| Body mass index, $kg/m^2$ | 22.1±0.7 | 20.6±0.6 |
| VC, % of pred. | 88.2±5.4 | 78.2±3.9 |
| IC, L | 1.89±0.12 | 1.71±0.12 |
| $FEV_1$, L | 1.16±0.09 | 1.12±0.11 |
| $FEV_1$, % of pred. | 46.1±3.9 | 42.7±3.6 |
| $FEV_1$/FVC, % | 47.2±2.8 | 44.5±2.4 |
| RV, % of pred. | 211.0±17.0 | 201.8±11.6 |
| TLC, % of pred. | 124.1±5.5 | 120.5±4.0 |
| RV/TLC, % | 55.3±2.3 | 55.8±2.4 |
| DLCO, % of pred. | 56.0±5.1 | 42.6±5.0 |

Table 2. Effects of SABA or SAMA on $FEV_1$ and respiratory impedance

| | SABA (n=16) | | SAMA (n=16) | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| $FEV_1$, L | 1.16±0.09 | 1.30±0.09** | 1.11±0.11 | 1.19±0.11** |
| Rrs5, kPa·s/L | 0.47±0.04 | 0.40±0.04** | 0.43±0.03 | 0.42±0.06 |
| Rrs5-Rrs20, kPa·s/L | 0.17±0.02 | 0.13±0.02* | 0.15±0.02 | 0.13±0.02 |
| Xrs5, kPa·s/L | -0.27±0.04 | -0.21±0.04 | -0.25±0.03 | -0.22±0.03 |
| ΔRrs5, kPa·s/L | 0.17±0.04 | 0.14±0.03 | 0.14±0.02 | 0.11±0.02 |
| ΔXrs5, kPa·s/L | 0.16±0.06 | 0.09±0.05 | 0.13±0.05 | 0.09±0.04 |
| $f$res, Hz | 27.0±1.7 | 23.9 ±1.5* | 26.2±1.1 | 24.7±1.2 |

Table 3. Effects of SABA or SAMA on the shuttle walking test

| | SABA (n=16) | | SAMA (n=16) | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| Walking distance, m | 281.9±21.1 | 301.3±21.3* | 347.8±26.0 | 345.4±25.7 |
| Lowest $SpO_2$, % | 88.7±1.4 | 88.1±1.3 | 85.9±1.5 | 85.6±1.3 |
| PRmax, beats/minute | 103.0±4.0 | 110.1±3.3 | 103.8±5.6 | 109.3±4.5 |
| BSmax | 4.9±0.6 | 5.1±0.6 | 5.8±0.3 | 6.1±0.3* |