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Effects of bronchodilators on dynamic hyperinflation following hyperventilation in patients with COPD.

Keisaku Fujimoto, MD [1)] *; Fumiaki Yoshiike, MD [1)]; Masanori Yasuo, MD [1)]; Yoshiaki Kitaguchi, MD [1)]; Kazuhisa Urushihata, MD [1)]; Keishi Kubo, MD [1)]; Takayuki Honda, MD [2)].

[1)] Department of Internal Medicine and [2)] Department of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto, 390-8621, JAPAN.

*Corresponding Author: Keisaku Fujimoto, MD

First, Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, 390-8621, Japan.

Tel: +81-263-37-2631, Fax: +81-263-36-3722

E-mail: keisaku@hsp.md.shinshu-u.ac.jp

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Abstract

Objectives. The present study was performed to examine the occurrence of dynamic hyperinflation following hyperventilation in COPD and ex-smokers without COPD and the efficacy of short-acting anti-cholinergic agents (SAAC) and β_2-agonists (SABA) for lung hyperinflation following metronome-paced hyperventilation in COPD.

Methodology. Fifty-nine patients with COPD, 20 ex-smokers without COPD, and 20 healthy subjects who had never smoked were examined for dynamic hyperinflation by metronome-paced hyperventilation increasing respiratory rate from 20 to 30 and 40 tidal breaths/min. Dynamic hyperinflation was evaluated as the decrease in inspiratory capacity (IC) following hyperventilation, and the effects of SAAC and SABA on dynamic hyperinflation.

Results. COPD patients showed a significant increase in end-expiratory lung volume (EELV) and decrease in IC following hyperventilation, and ex-smokers without COPD also showed mild and significant dynamic hyperinflation. Multiple stepwise linear regression analysis revealed that $DLco/V_A$ and RV/TLC were significant and independent determinants for dynamic hyperinflation in COPD. Treatment with SAAC and SABA significantly increased IC at each rate of breaths/min, independent of the increases in FEV_1. Furthermore, SABA significantly inhibited the decrease in IC by

hyperventilation.

Conclusions. These findings suggest that lung hyperinflation following hyperventilation may be a useful method to detect dynamic hyperinflation observed not only in patients with COPD but also in ex-smokers without COPD, and both SAAC and SABA are effective to reduce the dynamic hyperinflation in COPD.

Key Words: chronic obstructive pulmonary disease (COPD), hyperventilation, air trapping, lung hyperinflation, and bronchodilator.

Runnig Head: Effect of bronchodilator on dynamic hyperinflation.

Introduction

In COPD, exercise induces an increase in end-expiratory lung volume (EELV) corresponding to the increase in ventilation. This phenomenon has been called dynamic hyperinflation [1]. Dynamic hyperinflation is attributed to trapping of air during exercise caused by a decrease in elastic recoil pressure due to destruction of the alveoli and narrowing of the small airways [2, 3]. There is a significant relationship between dynamic hyperinflation and dyspnea on exercise or decreased exercise tolerance in COPD [2, 4]. The utility of repeated measurements of inspiratory capacity (IC) during exercise to reflect changes in EELV has been demonstrated [1, 5, 6], as total lung capacity (TLC) remains constant after acute bronchodilation and during exercise [7, 8]. O'Donnell *et al.* [9] confirmed that Borg dyspneic ratings and measurements of IC and endurance time during submaximal cycle exercise testing are highly reproducible and responsive to changes in severe COPD. Both β_2-agonists and anti-cholinergic agents have been shown to reduce the increase in EELV and the decrease in IC during exercise, which resulted in relief of dyspnea during exercise testing [10-12]. The relief of dynamic hyperinflation by treatment with bronchodilators may be due to improvement of airflow limitation.

Changes in IC are correlated with breathing frequency in patients with COPD [1]. Gelb *et al.* [13] compared metronome-paced hyperventilation with incremental

symptom-limited cycle ergometry to provoke respiratory rate-induced reduction of IC in patients with COPD, and demonstrated that both metronome-paced hyperventilation and incremental cycle ergometry, when respiratory rate doubled at rest, provoked similar significant decreases in IC, even after administration of aerosolized ipratropium bromide (IB). They concluded that the noninvasive simplicity of hyperventilation provides a clinically useful screening surrogate to monitor changes in IC following exercise. In this study, we modified the method of hyperventilation used by Gelb *et al.*, *i.e.*, respiratory rate was increased from metronome-paced 20 breaths/min to 40 breaths/min in 10 breaths/min increments, and IC was measured followed by 30 seconds of breathing at each breathing frequency. Furthermore, we also measured not only IC but also EELV by body plethysmography using a body box. The purpose in this study was not to simulate dynamic hyperinflation during exercise by metronome-paced incremental hyperventilation, but to evaluate dynamic hyperinflation quantitatively in ex-smokers without COPD and patients with COPD and to analyze the contributing factors to dynamic hyperinflation and to examine the effects of two different bronchodilators, a short-acting β_2-agonist (SABA) and short-acting anti-cholinergic agent (SAAC), on dynamic hyperinflation induced by incremental hyperventilation in COPD.

Materials and Methods

Subjects

Fifty-nine consecutive male patients with COPD admitted to our outpatient clinic from September 2004 to October 2005 consistent with the selection criteria were enrolled in the present study with informed consent. All cases were smoking-related COPD without α_1-antitrypsin deficiency, and all subjects had a smoking history of more than 30 packs×year. COPD was diagnosed based on a clinical history of exertional dyspnea, pulmonary function characterized by irreversible airway obstruction, lung hyperinflation, reduced gas transfer, and presence of anatomic emphysema on high-resolution computed tomography (HRCT). Irreversible airflow limitation is defined as $FEV_1/FVC<70\%$ after inhalation of a $ß_2$-agonist in accordance with the GOLD guidelines [14]. All patients with COPD were examined the reversibility by SABA prior to the study. Patients with any history of asthma, asthmatic symptoms, such as coughing or wheezing at rest in a stable phase, as well as those who had taken oral steroids or had suffered from respiratory tract infection or exacerbation during the preceding 3 months were excluded. The severity of COPD according to the GOLD guidelines [14] was as follows: 10 patients in stage 1, 22 in stage 2, 17 in stage 3, and 10

in stage 4. Twenty healthy male subjects who had never smoked ranging in age from 60 to 81 years, with a mean age of 68 years, who showed normal spirometry and 20 male ex-smokers without COPD ranging in age from 59 to 90 years, with a mean age of 68 years, were also enrolled in this study. The criteria of recruiting healthy volunteer who had never smoked was male, more than 60 years old, and normal spirometry, and the criteria of recruiting volunteers of ex-smoker was male, more than 60 years old, normal spirometry (vital capacity (VC) ≥80% and FEV_1/FVC ≥70%), and smoking history more than 30 packs×year. The study was approved by the local research ethics committee, and all patients gave their informed consent to participation.

Study Design

Patients were instructed to continue all their usual medications, but to withhold SABA and short-acting anti-cholinergic agents (SAAC) for 12 h and the long-acting β_2-agonist and anti-cholinergic agent (tiotropium) and tulobuterol tape for 24 h. After obtaining informed consent, all patients underwent pulmonary function tests including spirometry and measurements of DLco with a pulmonary function testing system (Chestac-55V; Chest Co. Ltd., Tokyo, Japan). Functional residual capacity (FRC) was measured by body plethysmography using a body box (Medgraphic, Ann Arbor, MI),

after which the subjects immediately inspired to total lung capacity (TLC) and expired maximally to residual volume (RV), thus allowing calculation of lung volume and RV/TLC. Concerning the predicted values for FEV_1 and VC, Japanese local reference [15] developed by Japanease Respiratory Society were adopted, and the predicted values for DLco were calculated from the formula developed by Nishida *et al.* for Japanese normal population [16]. The predicted values for FRC and RV measured by body plethysmography were determined by the formulas of Boren *et al.* [17]. Measurement of dynamic hyperinflation was performed by metronome-paced hyperventilation using the body box. End-expiratory lung volume (EELV) by body plethysmography, IC, and VC were measured immediately after breathing at a rate of 20 tidal breaths/min paced by a metronome for 30 seconds. Consequently, breathing rate was increased up to 30 tidal breaths/min and 40 tidal breaths/min in increments of 30 seconds, and EELV, IC and VC were again measured immediately after the procedure of metronome-paced hyperventilation for 30 seconds at each respiratory rate. We directed all subjects to maintain the tidal volume while watching spirogram with a monitor. After completion of the baseline measurements, the patients were divided into two groups at random. The patients of one group inhaled 20 μg of procaterol hydrochloride (SABA), while those in the other inhaled 0.2 mg of oxytropium bromide (SAAC) using a spacer. Spirometry to

determine dynamic hyperinflation by metronome-paced hyperventilation was again performed 30 min after inhalation of procaterol hydrochloride or 60 min after inhalation of oxytropium bromide. Pulmonary function test was performed by two special technicians according to the ATS criterion. Two or three tests were repeated to guarantee repeatability.

Data Analysis

The values shown in the text, tables, and figures are means±SEM. The data distribution of the variables among the groups was first assessed with Bartlett's test. When the data for the variables showed a normal distribution, they were compared by one-way analysis of variance (ANOVA), followed by multiple comparisons with the Tukey-Kramer method. When the data for the variables did not show a normal distribution, the variables were compared with the Kruskal-Wallis test, followed by multiple comparisons among groups with the nonparametric Tukey-Kramer method. Comparisons of variables at baseline and after the inhalation of bronchodilators were performed by paired *t*-tests. Simple ccorrelations between variables were examined by calculating Pearson's product correlation coefficient. Multiple, stepwise regression analysis was performed to identify which variables were significantly associated with

the decrease in IC following the metronome-paced hyperventilation. The $p<0.15$ was used first to identify candidate variables, and then removed variables from the regression model if p value was more than 0.1. All statistical analyses were performed with the use of a Windows-compatible software program (Stat Flex ver. 5.0, Artech Ltd., Osaka, Japan). A p value of less than 0.05 was considered significant for the results of all statistical analyses.

Results

There were no significant differences in age among the subjects who had never smoked, ex-smokers, and the two COPD patient groups administered SABA or SAAC (Table 1). The body mass index was significantly lower in COPD patients compared with those who had never smoked or ex-smokers. FEV_1 and FEV_1/FVC were within the normal range, but were significantly lower than those in the subjects who had never smoked. The MMEF (V_{75-25}; maximum mid expiratory flow rate) in ex-smokers without COPD was also significantly lower than in subjects who had never smoked. There were no significant differences in smoking history or pulmonary function between the two COPD groups.

The patients with COPD in the two groups showed significant higher values of EELV

and lower values of IC measured immediately after breathing at rates of 20, 30, and 40 tidal breaths/min with metronome pacing for 30 seconds compared with the subjects who had never smoked and ex-smokers without COPD (Table 2). The EELV measured at the rate of 20 tidal breaths/min ($EELV_{20}$) was significantly increased and the IC (IC_{20}) was significantly decreased followed by hyperventilation at rates of 30 ($EELV_{30}$ and IC_{30}) and 40 ($EELV_{40}$ and IC_{40}) tidal breaths/min both in ex-smokers without COPD and patients with COPD, and showed dynamic hyperventilation followed by hyperventilation. In COPD patients, IC was further decreased followed by hyperventilation at the rate of 40 tidal breaths/min. However, the EELV and IC in the subjects who had never smoked were not changed followed by hyperventilation at rates of 30 or 40 tidal breaths/min, and did not show any dynamic hyperinflation. In COPD patients, the decreases in IC at rates of 30 (ΔIC_{30}) and 40 (ΔIC_{40}) tidal breaths/min from the IC at the rate of 20 tidal breaths/min were the most prominent among the three groups and there were significant differences from those in subjects who had never smoked (Figure 1). In ex-smokers, the ΔIC_{40} was also significantly greater than that in subjects who had never smoked. In COPD, the % decrease in IC_{30} from IC_{20} showed a weak but significantly correlation with FEV_1 ($r=-0.29$, $p<0.05$), resting IC/TLC ($r=-0.29$, $p<0.05$), $DLco/V_A$ ($r=-0.28$, $p<0.05$), RV/TLC ($r=0.30$, $p<0.05$). Multiple

stepwise linear regression analysis also showed a significant regression model for the % decrease in IC_{30} from IC_{20} ($r=0.39$, $p<0.01$) comprised of $DLco/V_A$ ($p=0.04$) and RV/TLC ($p=0.02$) in COPD. This model accounted for 12.4% of the % decrease in IC_{30} from IC_{20}.

Administration of SABA or SAAC significantly increased FEV_1, but there was no difference in the increase of FEV_1 (SABA; 0.11±0.02 L, SAAC; 0.15±0.02 L) following administration of the two drugs. Inhalation of SABA resulted in significant decreases in $EELV_{20}$, $EELV_{30}$, and $EELV_{40}$ and significant increases in IC_{20}, IC_{30}, and IC_{40} (Table 3). The inhalation of SAAC also resulted in a significant decrease in $EELV_{20}$ and significant increases in IC_{20}, IC_{30}, and IC_{40}. However, the increased IC20, IC30 or IC40 or % increase in each IC values following the administration of SABA or SAAC did not significantly correlated with the increased FEV_1 or % increase in FEV_1 in the two groups, and the increases in IC_{20}, IC_{30}, and IC_{40} were independent of the increase in FEV_1. SABA administration also resulted in significant reduction of ΔIC_{30} and ΔIC_{40}, and significantly inhibited the decrease in IC followed by hyperventilation. However, SAAC administration resulted in no changes in ΔIC_{30} or ΔIC_{40}.

Discussion

In this study, patients with COPD showed a significant increase in EELV and decrease in IC, dynamic hyperinflation, following metronome-paced hyperventilation, and ex-smokers without COPD also showed mild and significant dynamic hyperinflation. Multiple stepwise linear regression analysis indicated that $DLco/V_A$ and RV/TLC were significant and independent determinants for dynamic hyperinflation in COPD. SABA and SAAC treatment significantly increased IC at 20, 30, and 40 tidal breaths/min without a significant correlation with the increases in FEV_1. Furthermore, SABA administration significantly inhibited the decrease in IC by increasing respiratory rates from 20 to 30 and from 20 to 40 tidal breaths/min. These findings suggest that lung hyperinflation dependent on increased rate of tidal breaths/min may be a useful method to detect dynamic hyperinflation quantitatively observed not only in patients with COPD but also in ex-smokers without COPD, and both SABA and SAAC are effective to reduce the dynamic hyperinflation in COPD.

Gelb *et al.* [13] reported that both metronome-paced hyperventilation and exercise by incremental cycle ergometry, when resting respiratory rate was doubled, provoked similar significant decreases in IC, and the noninvasive simplicity of hyperventilation provided a clinically useful screening surrogate to monitor changes in IC following exercise. They evaluated changes in IC by increasing resting respiratory rate by twofold.

However, the respiratory rate was different between individuals. The decrease in IC may be affected by baseline respiratory rates because the decrease in IC is dependent on respiratory rate [1)]. In this study, the changes in IC were evaluated by constantly increased respiratory rate from 20 to 40 tidal breaths/min in increments of 10 tidal breaths/min. Our method may be more quantitative because the respiratory rate increased incrementally is constant. On the other hand, the exercise response in terms of increase tidal volume and respiratory rate differs between normal subject and a patient with moderate to severe COPD. When a patient with moderate to severe COPD exerts, the respiratory rate will increase instead of the tidal volume due to the limitation of increase in tidal volume, whereas tidal volume will increase at first in normal subjects. Therefore, the metronome-paced hyperventilation may not simulate ventilatory response to exercise in healthy never smokers and ex-smokers without COPD. However, the maneuver of hyperventilation may be sensitive and quantitative to detect the presence of dynamic hyperinflation. In this study, ex-smokers without COPD also showed a slight but significant increase in EELV and decrease in IC following hyperventilation, but those who had never smoked did not. The ex-smokers had small airway disease because their MMEF (V_{75-25}; maximum mid expiratory flow rate) and V_{25}/HT were significantly decreased compared with those in the subjects who had

never smoked. Our colleagues have demonstrated that the average HRCT number at full expiration/full inspiration (E/I ratio) is significantly elevated in smokers without COPD compared with that in the subjects who had never smoked, and suggests the presence of air-trap on HRCT at full expiration even in smokers without COPD [18]. Suggesting from data of the HRCT findings, it may be reasonable that the ex-smokers without COPD also showed dynamic hyperinflation. These findings suggest that not only the patients with COPD but also ex-smokers without COPD show dynamic hyperinflation following hyperventilation, and the metronome-paced hyperventilation by constantly increased respiratory rate from 20 to 30 and 40 tidal breaths/min may be sensitive to detecting the presence of air-trapping.

Administration of inhaled short- or long-acting anti-cholinergic agent and β_2-agonist significantly increase IC at rest and during exercise, and reduce air-trapping and dynamic hyperinflation [5), 9), 11), 19), 20)]. However, Gelb *et al.* [13)] found no significant increases in IC at baseline or peak exercise after hyperventilation following administration of ipratropium bromide, in contrast to the results reported previously. In this study, the administration of oxytropium bromide significantly increased IC at 20, 30, or 40 tidal breaths/min as well as SABA administration. The increases in IC_{20}, IC_{30}, and IC_{40} after administration of bronchodilators were not significantly correlated with

improvement in FEV_1. Borg dyspnea rating during exercise is correlated better with the decrease in IC following exercise than with any other resting or exercise parameter [9], and also there is a significant correlation between improvement of exercise tolerance and the increase in IC during exercise after administration of anti-cholinergic agent, whereas the increased FEV_1 does not show any significant correlation with the improvement of exercise tolerance [21]. In this study, multiple, linear regression analysis showed that the dynamic hyperinflation by increasing respiratory rate was significantly determined by the decreased $DLco/V_A$ and increased RV/TLC, but not the decreased FEV_1. That is, the loss of elastic recoil pressure may have a large contribution to dynamic hyperinflation. These findings suggest that dynamic hyperinflation may be an important factor that causes dyspnea and decreases exercise tolerance as a factor independent of FEV_1. O'Donnell *et al.* reported that the sustained reduction of lung hyperinflation at rest and during exercise following treatment with bronchodilators increases in IC, which permits greater expansion of tidal volume and contributes to the improvements in both exertional dyspnea and exercise tolerance [11]. On the other hand, the SAAC, oxytropium bromide, did not inhibit the decrease in IC by increasing respiratory rates, whereas IC measured at each rate of tidal breaths/min was significantly increased. In contrast, the SABA, procaterol hydrochloride, significantly

reduced IC measured at each rate of tidal breaths/min and also inhibited the decreases in IC, whereas the increase in FEV_1 was not different between the two groups. The treatment with both the long-acting anti-cholinergic agent, tiotropium bromide, and the long-acting β_2-agonist, salmeterol xinafoate have been demonstrated to reduce not only static lung hyperinflation but also dynamic hyperinflation [11), 12)], and most of comparative studies between the two long-acting bronchodilators indicate that the effects of tiotropium on pulmonary function including resting IC, dyspnea, and QOL are superior to those of salmeterol xinafoate [22), 23)]. In this study, the reason for the difference in the effect on dynamic hyperinflation between the two drugs is unclear, however, both the two different bronchodilators were significantly increased IC at each tidal breaths/min and reduced dynamic hyperinflation induced by incremental hyperventilation.

In conclusion, our modified and simplified method of incremental metronome-paced hyperventilation may be sensitive to detect the presence of dynamic hyperinflation quantitatively, and demonstrated the presence of dynamic hyperinflation not only in patients with COPD but also in ex-smokers who did not have COPD and the efficacy of the different type of bronchodilators, SABA and SAAC, for dynamic hyperinflation.

References

1. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am Rev Resp Dis* 1993; **148**: 1351-1357.
2. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **164**: 770-777.
3. O'Donnell DE, D'Arsigny C, Fitzpatrick M, Webb KA. Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. *Am J Respi Crit Care Med* 2002; **166**: 663-668.
4. Diaz O, Villafranca C, Ghezzo H, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Respir J* 2000; **16**: 269-275.
5. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996 ; **153**: 967-975.
6. Dodd DS, Brancatisano T, Engel LA. Chest wall mechanics during exercise in patients with severe chronic airflow obstruction. *Am Rev Respir Dis* 1984; **12**:

33-38.

7. Stubbing DG, Pengelly LD, Morse JLC, et al. Pulmonary mechanics during exercisein subjects with chronic airflow obstruction. *J Appl Physiol* 1980; **49**: 511-515.

8. Duranti R, Filipelli M, Bianchi R, et al. Inspiratory capacity and decrease in lung hyperinflation with albuterol in COPD. *Chest* 2002; **122**: 2009-2014.

9. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **158**: 1557-65.

10. Michael L, et al.: Inhaled bronchodilators reduce dynamic Hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; **153**: 967-975.

11. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. *Eur Respir J* 2004; **23**: 832-840.

12. Man WDC, Mustfa N, Nikoletou D, Kaul S, Hart N, Rafferty GF, Donaldson N, Polkey MI, Moxham J. Effect of salmeterol on respiratory muscle activity during exercise in poorly reversible COPD. *Thorax* 2004; **59**: 471-476.

13. Gelb AF, Gutierrez CA, Weisman IM, Newsom R, Taylor CF, Zamel N. Simplified detection of dynamic hyperinflation. *Chest* 2004; **126**: 1855-1860.

14. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: Executive summary updated 2003 based on an April 1998 NHLBI/WHO workshop. 2003.

15. Spirometry, Flow-volume curve, Diffusion capacity of the lung. The Japanese Respiratory Society. Tokyo, 2004.

16. Nishida, et al. Nishida O, Kambe M, Sewake N, et al. Pulmonary function in healthy subjects and its prediction: 5. Pulmonary diffusing capacity in adults. *Jpn J Clin Pathol* 1976; **24**: 941-947.

17. Boren HG, Kory RC, Syner LC, et al. The veterans administration-army cooperative study of pulmonary function. 2. The lung volume and its subdivisions in normal men. *Am J Med* 1966; **41**: 96-101.

18. Kubo K, Eda S, Yamamoto H, Fujimoto K, Matsuzawa Y, Maruyama Y, Hasegawa M, Sone S, Sakai F: Expiratory and inspiratory chest computed tomography and pulmonary function tests in cigarette smokers. *Eur Respir J* 1999; **13**:252-256.

19. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;

24: 86-94.

20. Boni E, Corda L, Franchini D, et al. Volume effect and exertional dyspnea after bronchodilator in patients with COPD with and without expiratory flow limitation at rest. *Thorax* 2002; **57**: 528-32.
21. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **160**: 42-549.
22. Brusasco, V, Hodder R, Miravitlles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; **58**: 399-404.
23. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; **122**: 47-55.

Table 1. Characteristics of healthy subjects who had never smoked, ex-smokers without COPD, and two COPD patient groups administered β_2-agonist or anti-cholinergic agent.

	Never SM	Ex-SM	β_2-agonist Gp	Anti-cholinergic Gp
Number	20	20	30	29
Age, yr	68±1	68±2	71±1	70±1
BMI, kg/m^2	23.0±0.7	23.8±1.0	20.9±0.5 *††	21.1±0.5 *†
Smoking, pack×year	0	40.1±4.2	57.0±3.7 ††	60.5±4.3 ††
VC, % of pred.	107.5±6.3	111.2±3.2	94.9±4.8	100.6±2.9
FEV_1, % of pred.	110.5±5.8	98.9±2.8 *	51.9±4.3 **††	56.8±3.5 **††
FEV_1/FVC, %	83.0±1.6	77.7±1.0 **	47.8±1.8 **††	49.0±2.4 **††
V_{75-25}, % of pred.	93.6±5.2	77.8±3.9 *	22.7±2.5 **††	24.8±2.5 **††
V_{25}/HT, % of pred.	74.2±7.5	48.0±2.9 **	17.3±1.8 **††	16.1±1.3 **††
FRC, % of pred.	119.1±4.1	108.1±3.7	126.2±5.5 **††	127.1±6.3 **††
RV, % of pred.	126.3±6.1	140.9±8.8	202.6±11.4 **††	198.2±12.1 **††
TLC, % of pred.	113.8±2.9	113.3±3.4	129.3±5.8 **††	128.7±5.2 **††
RV/TLC, %	34.2±1.7	38.0±1.4	52.2±2.0 **††	49.3±1.9 **††
DLco, % of pred.	93.1±2.3	86.9±5.4	54.4±4.2 **††	56.3±4.1 **††
PaO_2, Torr	–	–	71.0±1.9	71.9±2.1
$PaCO_2$, Torr	–	–	40.7±0.9	40.6±0.9

Values are means ± SEM. BMI; body mass index, Gp; group. *p<0.05 and **p<0.01 vs. never smokers; subjects who had never smoked. †p<0.05 and ††p<0.01 vs ex-smokers without COPD.

Table 2. Changes in end-expiratory lung volume (EELV) and inspiratory capacity (IC) following respiration at 20, 30, and 40 tidal breaths/min for 30 seconds with metronome pacing in subjects who had never smoked, ex-smokers without COPD, and patients with COPD.

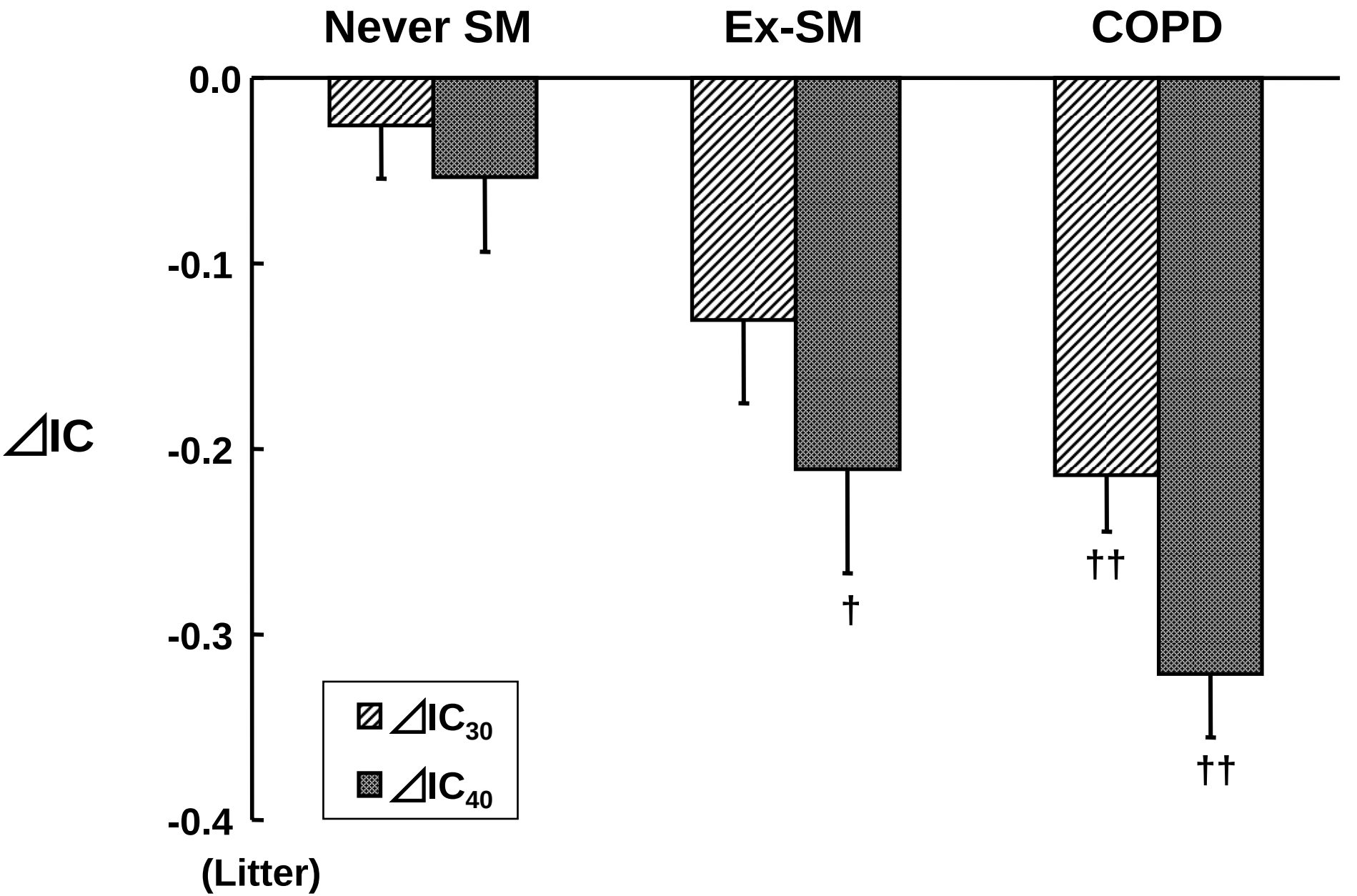
	Never SM	Ex-SM	COPD
Number	20	20	59
$EELV_{20}$, L	3.25±0.15	3.59±0.21	4.72±0.15 †† §
$EELV_{30}$, L	3.37±0.17	3.83±0.24 *	4.85±0.16 * †† §
$EELV_{40}$, L	3.32±0.16	3.85±0.19 *†	4.91±0.16 * †† §
IC_{20}, L	2.15±0.13	2.45±0.09	1.75±0.07 †† §
IC_{30}, L	2.12±0.14	2.32±0.10 **	1.54±0.07 ** †† §
IC_{40}, L	2.09±0.13	2.24±0.09 **	1.43±0.07 **¢ †† §
$\triangle IC_{30}$, L	-0.03±0.03	- 0.13±0.04	- 0.21±0.03 ††
$\triangle IC_{40}$, L	-0.05±0.04	- 0.21±0.06 †	- 0.32±0.03 ††

Values are means±SEM. △IC30 and △IC40; the decreases in IC at rates of 30 and 40 tidal breaths/min from the IC at the rate of 20 tidal breaths/min.
***p<0.05 and **p<0.01 vs. 20 breaths/min, ¢p<0.05 vs. 30 breaths/min, †p<0.05 and ††p<0.01 vs. never smoker (SM), §p<0.01 vs. ex-smoker (SM).**

Table 3. Effects of inhaled short-acting β_2-agonist and short-acting anti-cholinergic agent on end-expiratory lung volume (EELV) and inspiratory capacity (IC) following respiration at 20, 30, and 40 tidal breaths/min for 30 seconds.

	β_2-agonist Gp (n=30)		Anti-cholinergic Gp (n=29)	
	Pre	Post	Pre	Post
FEV_1, L	1.43±0.11	1.54±0.12 **	1.52±0.11	1.67±0.11 **
FVC, L	2.84±0.16	3.09±0.15 **	3.10±0.10	3.25±0.10 **
$EELV_{20}$, L	4.80±0.22	4.47±0.20 **	4.64±0.21	4.48±0.19 *
$EELV_{30}$, L	4.92±0.22	4.50±0.20 **	4.78±0.23	4.61±0.20
$EELV_{40}$, L	4.95±0.25	4.62±0.21 *	4.87±0.20	4.74±0.19
IC_{20}, L	1.77±0.10	1.86±0.10 *	1.81±0.10	1.94±0.10 *
IC_{30}, L	1.51±0.11	1.68±0.10 **	1.64±0.11	1.76±0.09 *
IC_{40}, L	1.41±0.10	1.64±0.10 **	1.50±0.10	1.63±0.09 *
$\triangle IC_{30}$, L	- 0.26±0.04	- 0.18±0.03 *	- 0.17±0.04	- 0.18±0.04
$\triangle IC_{40}$, L	- 0.36±0.05	- 0.23±0.05 *	- 0.31±0.05	- 0.31±0.06

Values are means ±SEM. $\triangle IC_{30}$ and $\triangle IC_{40}$; the decreases in IC at rates of 30 and 40 tidal breaths/min from the IC at the rate of 20 tidal breaths/min.
$^{*}p<0.05$ and $^{**}p<0.01$ *vs*. pre-treatment.


Never SM
Ex-SM
COPD
0.0
-0.1
-0.2
-0.3
-0.4
⊿IC
(Litter)
⊿IC30
⊿IC40
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