

Tiotropium Attenuates Refractory Cough and Capsaicin Cough Reflex Sensitivity in Patients with Asthma



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What is already known about this topic? Asthmatic cough is often refractory to standard treatments such as inhaled corticosteroids (ICS) and long-acting β_2 agonists (LABA). Recent study has shown that tiotropium may alter cough reflex sensitivity in patients with acute viral cough.

What does this article add to our knowledge? Tiotropium may ameliorate chronic asthmatic cough refractory to ICS and LABA by modulating capsaicin cough reflex sensitivity without affecting bronchomotor tone.

How does this study impact current management guidelines? Tiotropium may be preferable to other controllers as add-on medication in patients with asthma with chronic cough refractory to ICS and LABA.

BACKGROUND: Asthmatic cough is often refractory to standard treatments such as inhaled corticosteroids (ICS) and long-acting β_2 agonists (LABA). Tiotropium may modulate cough reflex sensitivity of acute viral cough, but its efficacy in asthmatic cough remains unknown.

OBJECTIVE: To evaluate whether tiotropium improves cough and cough reflex sensitivity in patients with asthma refractory to ICS/LABA.

METHODS: Seventeen consecutive patients with asthma with chronic cough despite the use of ICS/LABA (13 women; 43.4 $\pm$ 19.0 years; average ICS dose, 651 $\pm$ 189 μ g/d; fluticasone equivalent) were additionally treated with tiotropium (5 μ g/d) for 4 to 8 weeks to examine its effects on pulmonary function and capsaicin cough reflex sensitivity (cough thresholds C2 and C5). Cough severity, cough-specific quality of life, and

asthma control were also evaluated using cough visual analog scales (VASs), the Japanese version of Leicester Cough Questionnaire (J-LCQ), and Asthma Control Test (ACT), respectively. Patients with an improved cough VAS score of 15 mm or more were considered responders to tiotropium. **RESULTS:** Tiotropium significantly improved cough VAS, J-LCQ, and ACT scores, but not FEV₁. Changes in cough VAS score correlated with those in C2 ($r = -0.58$; $P = .03$), C5 ($r = -0.58$; $P = .03$), and ACT scores ($r = -0.62$; $P = .02$), but not in FEV₁ in the overall patients. When analyses were confined to the 11 responders, tiotropium significantly improved capsaicin cough reflex sensitivity within the subgroup (C2: $P = .01$ and C5: $P = .02$) and versus the nonresponders (C2: $P = .004$ and C5: $P = .02$).

CONCLUSION: Tiotropium may alleviate asthmatic cough refractory to ICS/LABA by modulating cough reflex sensitivity but not through bronchodilation. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1613-20)

Key words: Chronic asthmatic cough; Capsaicin cough reflex sensitivity; Tiotropium; Cough severity; Cough-specific quality of life

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INTRODUCTION

Cough is a common and troublesome symptom in patients with asthma. A previous study using conscious guinea pigs found that bronchoconstriction induced by methacholine inhalation triggered cough via stimulation of rapidly adapting receptors,¹ indicating that mechanical stress by bronchoconstriction induces cough. In accordance with this finding, a clinical study

Abbreviations used

ACT- Asthma Control Test

ICS- Inhaled corticosteroids

J-LCQ- Japanese version of Leicester Cough Questionnaire

LABA- Long-acting β_2 agonists

QOL- Quality of life

TRPV-1- Transient receptor potential vanilloid-1

VAS- Visual analog scale

showed that cough in subjects with asthma was caused by inhaled methacholine.² Therefore, asthmatic cough responds to bronchodilators, such as long-acting β_2 agonists (LABA), as well as inhaled corticosteroids (ICS).^{3,4} A recent study has revealed that capsaicin cough reflex sensitivity in patients with classical asthma is associated with the pathophysiology of cough, which is independent of airway eosinophilic inflammation, airway hyperresponsiveness, and lung function.⁵ These findings indicate that neurogenic inflammation is involved in the development of asthmatic cough,⁵ which may be related to asthma being refractory to classical treatments such as ICS and LABA. Indeed, up to 50% of patients with asthma suffer from persistent cough despite receiving adequate doses of ICS or LABA.^{6,7} Thus, cough reflex sensitivity may be associated with the development of chronic asthmatic cough, at least in a subset of these patients. For the treatment of cough reflex hypersensitivity, leukotriene receptor antagonists improved cough reflex sensitivity in patients with steroid-naïve cough-variant asthma.⁸ However, treatment for cough reflex sensitivity in patients with asthma receiving ICS or ICS with LABA (ICS/LABA) is not well established.

Acetylcholine is released from airway nerve terminals and structural cells, such as airway epithelium and smooth muscle cells, in response to cigarette smoking⁹ and allergen exposure.¹⁰⁻¹² It is also associated with the pathophysiology of asthma. Both *in vitro* and *ex vivo* studies in animal models have shown that acetylcholine contributes to bronchoconstriction,^{13,14} mucus hypersecretion,¹⁵ airway inflammation, and remodeling,¹⁰ which are primarily mediated via muscarinic M_3 receptors. Tiotropium, an inhaled muscarinic M_3 receptor antagonist, inhibits such cholinergic effects in experimental studies.^{11,12,16} It also improves lung function^{17,18} and decreases exacerbations¹⁸ in patients with uncontrolled asthma.

Regarding the development of asthmatic cough, acetylcholine and cholinergic nerves may contribute to the pathophysiology, because asthmatic cough is generally triggered by bronchoconstriction as a vagal nerve phenomenon.^{19,20} Recent studies have shown that tiotropium may alter cough reflex sensitivity.^{21,22} In naive guinea pigs, tiotropium improved cough reflex sensitivity by modulating transient receptor potential vanilloid-1 (TRPV-1).²¹ In patients with acute upper respiratory tract infection, capsaicin cough reflex hypersensitivity was alleviated by tiotropium without affecting lung function.²² Thus, tiotropium may have antitussive effects by altering cough reflex sensitivity.²¹⁻²³ However, the efficacy of tiotropium for chronic asthmatic cough remains poorly known.

We hypothesized that tiotropium could ameliorate chronic asthmatic cough refractory to ICS/LABA through the improvement of capsaicin cough reflex sensitivity. We evaluated the effects of tiotropium on capsaicin cough reflex sensitivity, lung function, and subjective measures of cough and asthma control

in patients with asthma with persistent cough despite the use of ICS/LABA.

METHODS**Patients**

Among patients who visited our asthma and cough outpatient clinic at Nagoya City University between April 2015 and March 2017, 17 consecutive patients with asthma with chronic cough persisting for 8 weeks or more despite the combination therapy with ICS/LABA were eligible for this study. All patients were previously diagnosed as having asthma on the basis of a history of characteristic symptoms, such as wheezing, shortness of breath, chest tightness, and cough that changed over time and in intensity, and the presence of bronchodilator reversibility and/or airway hyperresponsiveness.²⁴ They received tiotropium bromide (Spiriva respimat; Boehringer Ingelheim, Ingelheim am Rhein, Germany) 5 μ g once daily by inhalation, in addition to their present medications for 4 to 8 weeks. They underwent spirometry, capsaicin challenge test, and subjective measures of cough and asthma control on the days of starting and ending tiotropium treatment.

Patients who were currently smoking, had a smoking history of more than 10 pack-years, had stopped smoking within 6 months, or had other respiratory diseases were excluded from this study. In addition, patients who had already taken inhaled anticholinergic agents or medicines with anticholinergic effects, such as tricyclic antidepressants and antipsychotics, or had closed-angle glaucoma and benign prostate hypertrophy with urinary retention were not included. This study was approved by the Institutional Review Board of Nagoya City University.

Atopic predisposition

Total and specific IgE measurements taken before the study enrollment were used to determine the presence or absence of atopic predisposition. Specific IgE titers were measured against allergens such as house dust mites, Japanese cedar pollen, Japanese cypress, mixed graminea pollens (orchard grass, sweet vernal grass, Bermuda grass, timothy, and reeds), mixed weed pollen (ragweed, mugwort, goldenrod, dandelion, and oxeye daisy), *Trichophyton rubrum*, mixed molds (*Candida*, *Penicillium*, *Alternaria*, *Aspergillus*, *Helminthosporium*, and *Cladosporium*), cat dander, and dog dander (ImmunoCAP, Phadia K.K., Tokyo, Japan). If patients were sensitized to 1 or more allergens, they were considered atopic.²⁵

Spirometry

Spirometry was performed between 9 AM and 1 PM using Chestac-8900 (Chest, Tokyo, Japan) to measure FEV₁ and FEV₁% predicted according to the American Thoracic Society/European Respiratory Society guideline.²⁶

Capsaicin challenge test

After spirometry, capsaicin challenge test was performed between 9 AM and 1 PM. There are 2 methods for multiple dose-response capsaicin inhalation challenge: the classical single breath (dosimeter) method and the fixed-time inhalation method.²⁷ The fixed-time capsaicin inhalation (15 seconds), known as the tidal breathing method, using a Bennett Twin nebulizer (3012-60 cc, Puritan-Bennett Company, Carlsbad, Calif) was first reported by Fujimura et al.²⁸ This method was validated in comparison with the dosimeter method by the same group.²⁹ Our group has adapted the dose-response fixed-time method using Astograph (Chest),^{8,30,31} an apparatus to measure airway hyperresponsiveness (see Figures E1 and E2 in this article's Online

Repository at www.jaci-inpractice.org). This method was also previously validated in comparison with the original tidal breathing method of Fujimura et al, and has been widely used by other groups.^{32,33} With this method, each concentration of capsaicin is inhaled for 15 seconds, followed by saline inhalation for 45 seconds, at 1-minute intervals for 10 doubling concentrations (0.61-312 μ M). Saline inhalation is interspersed for increasing blindness to patients. As in the dosimeter method, the capsaicin concentrations by which at least 2 or 5 coughs were induced were defined as cough thresholds C2 or C5, respectively.

Subjective measures of cough and asthma control

Cough severity and cough-specific quality of life (QOL) were evaluated using the cough visual analog scale (VAS) and the Japanese version of Leicester Cough Questionnaire (J-LCQ), respectively.

Cough VAS is a 100-mm linear scale where its length represents cough severity: 0 mm indicates no cough and 100 mm indicates the worst cough imaginable.^{25,34} When patients showed an improvement of 15 mm or more on the cough VAS after the tiotropium treatment, they were considered responders.³⁵

Cough-specific QOL was evaluated using the J-LCQ, which was translated from the original version and validated.^{25,36} It consists of 19 questions covering 3 subdomains (physical, social, and psychological); total scores range from 3 to 21, with higher scores indicating better QOL.³⁶ Previous studies demonstrated a significant correlation between the J-LCQ and subjective cough severity and frequency.²⁵

The Asthma Control Test (ACT) was also completed. It is a self-administered questionnaire consisting of 5 item instruments, each item rated on a 5-point scale.³⁷ The questions address symptoms such as shortness of breath, cough, or wheezing, and the use of rescue medication in 4 weeks before the evaluation, with high scores indicating better asthma control.³⁷ When ACT total scores are less than 20, patients are considered poorly controlled.³⁷

Statistical analysis

Statistical analyses were performed using JMP 12.2 (SAS Institute Inc, Tokyo, Japan). Data are presented as mean $\pm$ SD. Data with nonnormal distribution are presented as median (range), except for C2 and C5, which are presented as mean $\pm$ SD after log-transformation. Clinical variables including cough VAS, J-LCQ, and ACT scores, FEV₁, and cough thresholds (log-transformed C2 and C5) before and after the tiotropium treatment were analyzed using the paired *t* test or the chi-square test. Correlations between changes in clinical variables such as subjective cough measures, cough thresholds, and FEV₁ were analyzed using the Pearson correlation test. Finally, factors associated with responders were estimated using univariate regression analysis. *P* values of less than .05 were considered statistically significant.

RESULTS

Overall patients' characteristics

The characteristics of all 17 patients are presented in Table I. Mean age was 43.4 $\pm$ 19.0 years, and 13 (76%) patients were women. Five patients had a smoking history of 2.0 $\pm$ 5.2 pack-years. None had received oral corticosteroids. Mean ACT scores were 17.6 $\pm$ 3.0, and 82% of patients were considered poorly controlled, mainly because of a persistent cough. Other symptoms such as wheezing and nocturnal shortness of breath were stable before the treatment with tiotropium.

TABLE I. Overall patients' characteristics and clinical indices before and after the tiotropium treatment

Characteristic	Before	After	<i>P</i> value
Age (y)	43.4 $\pm$ 19.0	—	—
Sex (male/female), n	4/13	—	—
Smoking status (never/ex-smoker), n	12/5	—	—
Body mass index (kg/m ²)	22.4 $\pm$ 4.3	—	—
Atopic, n (%)	8 $\pm$ 47	—	—
Total IgE (IU/L), median (range)	144 (5-1620)	—	—
Cough duration (mo), median (range)	6 (2-66)	—	—
ICS dose (FP equivalent) (μ g)	651 $\pm$ 189	—	—
Treatment with LTRA, n (%)	8 $\pm$ 47	—	—
Cough VAS score (mm)	53.3 $\pm$ 19.2	25.8 $\pm$ 25.6	.0005
J-LCQ score	12.8 $\pm$ 3.5	16.3 $\pm$ 3.2	.005
ACT score	17.6 $\pm$ 3.0	20.5 $\pm$ 4.1	.04
C2 (μ M)*	0.53 $\pm$ 0.61	0.62 $\pm$ 0.62	.54
C5 (μ M)*	0.60 $\pm$ 0.67	0.79 $\pm$ 0.68	.17
FEV ₁ (mL)	2991 $\pm$ 1008	3034 $\pm$ 1012	.39
%FEV ₁ predicted	104 $\pm$ 11	107 $\pm$ 13	.21

FP, Fluticasone propionate; LTRA, leukotriene receptor antagonist.

Note. Values are mean $\pm$ SD, unless otherwise indicated.

*Log-transformed.

The cough-related characteristics of the patients are presented in Table I. Median cough duration was 6 (range, 2-66) months. Cough VAS and J-LCQ scores before the treatment with tiotropium were 53.3 $\pm$ 19.2 mm and 12.8 $\pm$ 3.5, respectively. Log-transformed C2 and C5 were 0.53 $\pm$ 0.61 and 0.60 $\pm$ 0.67 μ M, respectively. As previously reported,³⁸ C2 and C5 in women were significantly lower than those in men (Figure 1, A). On the basis of the tests for specific aeroallergens, 8 (47%) patients were considered atopic. C2 and C5 in nonatopic patients were significantly lower than those in atopic patients (Figure 1, B). J-LCQ scores before the tiotropium treatment indicate severity similar to that reported in previous studies of chronic cough.^{25,39}

Efficacy of tiotropium in chronic asthmatic cough refractory to ICS/LABA in the complete patient cohort

First, the effects of tiotropium were assessed across the overall cohort of patients (Table I). Although pulmonary function did not change after the treatment, tiotropium significantly improved subjective cough measures (Figure 2) and asthma control. The analysis of variables related to subjective cough measures revealed that changes in cough VAS score were significantly correlated with those in capsaicin cough reflex sensitivity (Figure 3) and asthma control ($r = -0.62$; $P = .02$) but not with those in pulmonary function ($r = -0.34$; $P = .22$). Changes in J-LCQ scores were also associated with those in ACT scores ($r = 0.79$; $P = .0008$). There was no association between changes in J-LCQ scores and those in capsaicin cough reflex sensitivity (C2: $r = 0.35$; $P = .16$; C5: $r = 0.42$; $P = .09$). In addition, changes in pulmonary function were not correlated with those in capsaicin cough reflex sensitivity (C2: $r = -0.24$; $P = .41$; C5: $r = 0.27$; $P = .34$). These results suggest that

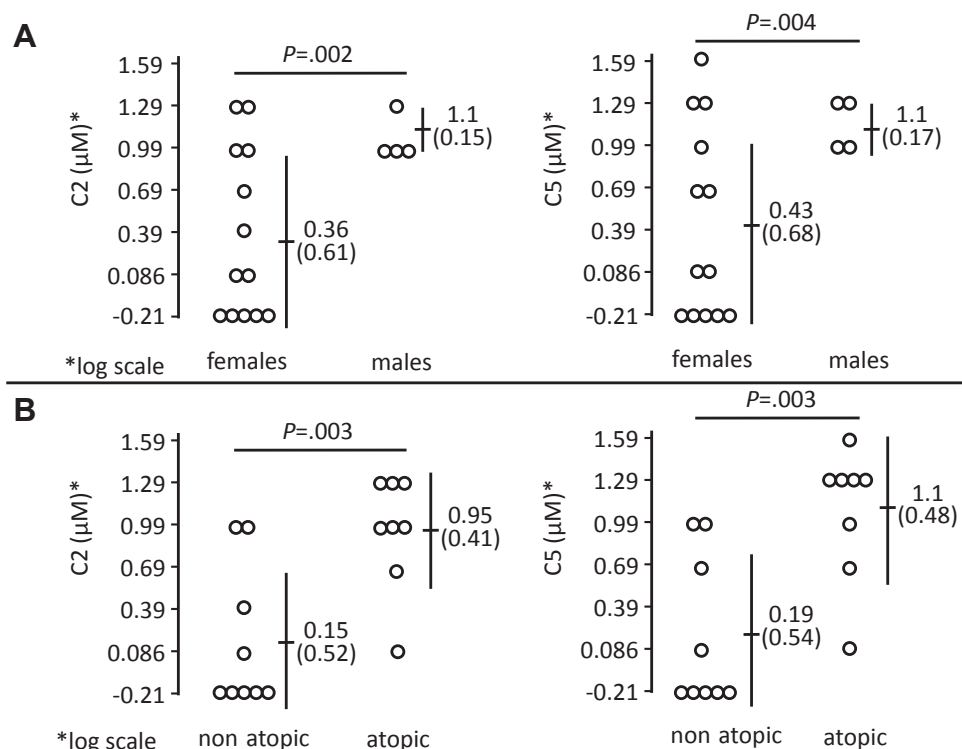


FIGURE 1. Cough thresholds before the initiation of tiotropium. (A) Female vs male and (B) nonatopic vs atopic patients. Horizontal and vertical bars indicate mean and SD, respectively.

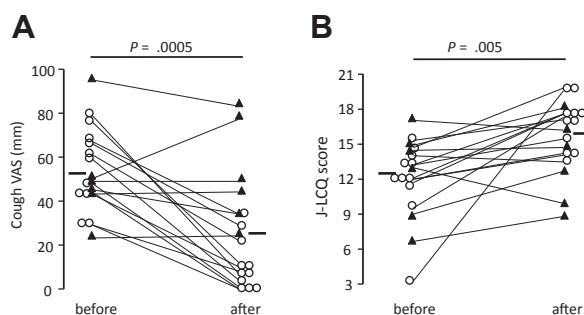


FIGURE 2. Subjective cough measurement after the tiotropium treatment. (A) Cough VAS and (B) J-LCQ. Open circles and closed triangles represent the responders and the nonresponders, respectively. Horizontal bars indicate mean.

tiotropium ameliorates cough severity by modulating capsaicin cough reflex sensitivity without affecting bronchomotor tone.

Efficacy of tiotropium in responders versus nonresponders

Next, we compared the efficacy of tiotropium between the responders (ie, patients who showed an improvement of ≥ 15 mm on the cough VAS) and the nonresponders (Table II). Clinical indices before the tiotropium treatment were similar between the 2 groups, including C2 ($P = .15$) and C5 ($P = .13$) (P values of other data not shown). When the analyses were confined to the responders, the tiotropium treatment significantly improved capsaicin cough reflex sensitivity (Figure 4) as

well as subjective cough measures and ACT scores (Table II). Pulmonary function did not change even in the responders. Changes in the capsaicin cough reflex sensitivity (Figure 4) and the J-LCQ and ACT scores (Table II) in the responders were significantly larger than those in the nonresponders.

No clinical indices at baseline including atopic predisposition and sex were associated with responsiveness to tiotropium (data not shown).

DISCUSSION

To our knowledge, this is the first report to demonstrate the efficacy of tiotropium in chronic asthmatic cough refractory to ICS/LABA. This study showed that tiotropium ameliorated cough severity, which was associated with changes in capsaicin cough reflex sensitivity. When analyses were confined to the responders, tiotropium significantly improved capsaicin cough reflex sensitivity within the subgroup and versus the nonresponders. These findings indicate that tiotropium may alleviate asthmatic cough refractory to ICS/LABA by modulating capsaicin cough reflex sensitivity.

The pathogenesis of asthmatic cough has been attributed to bronchoconstriction but not to cough reflex hypersensitivity.^{1,40} However, accumulating evidence has demonstrated that cough reflex sensitivity in patients with asthma is significantly higher than that in healthy subjects even if their cough symptoms are stable.^{5,41} A recent study has revealed that capsaicin cough reflex sensitivity in patients with classical asthma is associated with the development of cough, which is independent of lung function, airway eosinophilic inflammation, and airway hyper-responsiveness.⁵ In particular, exaggerated capsaicin-evoked

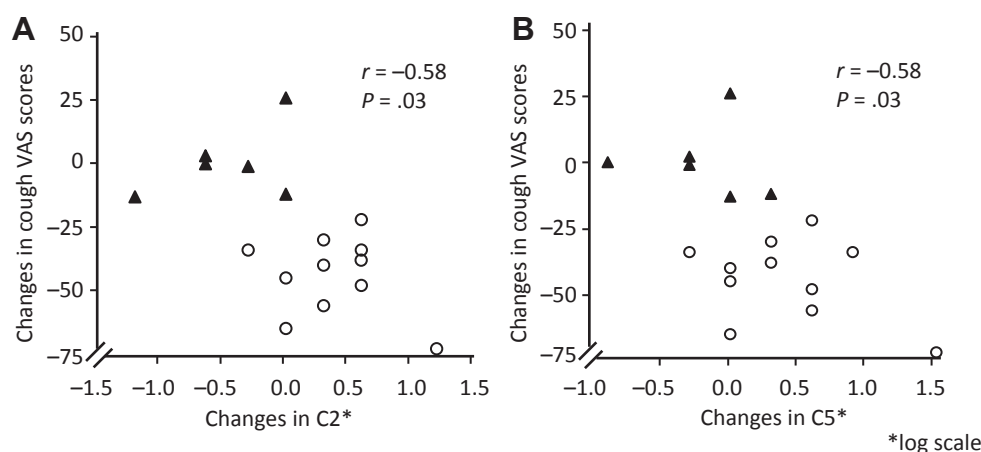


FIGURE 3. Correlations between changes in cough VAS score and those in capsaicin cough reflex sensitivity. (A) C2 and (B) C5. Open circles and closed triangles represent the responders and the nonresponders, respectively. Data of C2 and C5 are shown in log scale.

TABLE II. Clinical indices before and after the tiotropium treatment between the responders and the nonresponders

Characteristic	Responders (n = 11)			Nonresponders (n = 6)			P value*
	Before	After	P value	Before	After	P value	
Age (y)	45.2 ± 16.4	—	—	45.7 ± 25.0	—	—	—
Sex (male/female), n	2/9	—	—	2/4	—	—	—
Smoking status (never/ex-smoker), n	9/2	—	—	3/3	—	—	—
Body mass index (kg/m ²)	22.7 ± 5.0	—	—	21.8 ± 2.6	—	—	—
Atopic, n (%)	5 ± 46	—	—	3 ± 50	—	—	—
Total IgE (IU/L), median (range)	289 (5-1620)	—	—	37.6 (5-705)	—	—	—
Cough duration (mo), median (range)	6 (3-66)	—	—	18 (2-54)	—	—	—
ICS dose (FP equivalent) (μg)	650 ± 204	—	—	653 ± 183	—	—	—
Treatment with LTRA, n (%)	4 ± 37	—	—	4 ± 67	—	—	—
Cough VAS score (mm)	54.6 ± 17.3	11.5 ± 11.8	<.0001	50.8 ± 23.8	51.8 ± 23.5	.87	<.0001
J-LCQ score	12.5 ± 3.4	17.5 ± 2.2	.006	13.2 ± 4.1	14.1 ± 3.7	.44	.04
ACT score	16.6 ± 2.3	21.8 ± 4.1	.01	18.8 ± 3.5	18.8 ± 3.9	1.00	.03
C2 (μM)†	0.36 ± 0.56	0.74 ± 0.60	.01	0.84 ± 0.62	0.39 ± 0.63	.06	.004
C5 (μM)†	0.41 ± 0.64	0.83 ± 0.65	.02	0.94 ± 0.64	0.74 ± 0.79	.29	.02
FEV ₁ (mL)	2918 ± 995	2972 ± 950	.24	3083 ± 1112	3115 ± 1177	.81	.81
%FEV ₁ predicted	102 ± 9.2	105 ± 11.4	.11	108 ± 13.2	109 ± 16.5	.74	.67

FP, Fluticasone propionate; LTRA, leukotriene receptor antagonist.

Note. Values are mean ± SD, unless otherwise indicated.

*Comparison of the differences in clinical values between the responders and the nonresponders.

†Log-transformed.

cough response was observed in nonatopic and female patients with asthma.⁵ In the present study, capsaicin cough reflex sensitivity in nonatopic and female patients was significantly higher than that in atopic and male patients. Our data support the findings from Satia et al⁵ that cough reflex sensitivity is associated with the development of asthmatic cough.

Physiologically, capsaicin is used to measure cough reflex sensitivity as a TRPV-1 agonist.⁵ TRPV-1 is a nonselective ion channel expressed in sensory nerve fibers innervating the airway epithelium, which mainly originate in the jugular vagal ganglia.⁴² In a histological study of patients with chronic cough including patients with asthma, TRPV-1 expression was increased in the airways and was associated with capsaicin cough reflex hypersensitivity.⁴³ The increased expression of TRPV-1 in the airways

of patients with asthma with persistent cough may be associated with the development of heightened cough reflex sensitivity, which may contribute to the pathophysiology of chronic cough refractory to classical treatments for asthma including ICS/LABA. Thus, heightened cough reflex sensitivity in patients with asthma may be a new therapeutic target for persistent cough refractory to ICS/LABA.

Treatment for cough reflex hypersensitivity in patients with asthma who receive ICS/LABA is not well established. Recently, antitussive effects of tiotropium have been reported.^{21,22,44,45} Tiotropium improved cough symptoms in patients with diffuse panbronchiolitis⁴⁴ and in those with pediatric asthma.⁴⁵ In addition, tiotropium alleviated capsaicin cough reflex sensitivity without affecting lung function in patients with acute viral

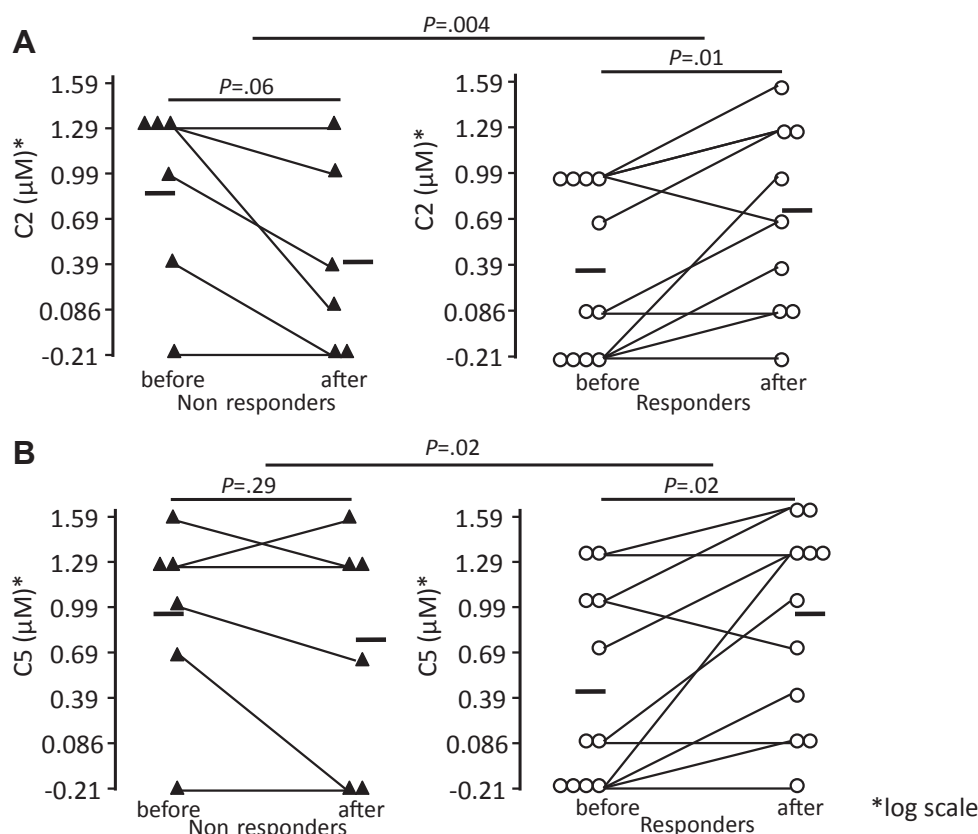


FIGURE 4. Changes in (A) C2 and (B) C5 after the tiotropium treatment between the responders and the nonresponders. Open circles and closed triangles represent the responders and the nonresponders, respectively. Data of C2 and C5 are shown in log scale. Horizontal bars indicate mean.

cough.²² In naive guinea pigs, tiotropium attenuated capsaicin-induced cough.²¹ In addition, tiotropium, but not other anticholinergics such as atropine and glycopyrrolate, inhibited capsaicin-, prostaglandin E₂-, and resiniferatoxin-induced depolarization of the isolated vagal sensory nerves.²¹ These findings suggest that tiotropium suppressed TRPV-1-mediated neural activities, independent of anticholinergic class effects.²¹ Consistent with previous studies, we demonstrated that tiotropium ameliorated cough severity through the improvement of capsaicin cough reflex sensitivity in patients with asthma with persistent cough refractory to ICS/LABA. This amelioration of chronic cough might be the effect of tiotropium as a TRPV-1 antagonist, but additional basic and histological studies will be necessary to confirm this hypothesis.

Tiotropium improves lung function in patients with asthma who have already received ICS/LABA.^{17,18} However, in the present study, FEV₁ did not significantly change even in the responders to tiotropium. That may be because the responders as well as nonresponders already treated with LABA showed nearly normal pulmonary function before the study enrollment, and there was no room for the improvement by the bronchodilator effect of tiotropium. In the present study, changes in pulmonary function were not correlated with those in either cough severity or capsaicin cough reflex sensitivity. Likewise, in patients with acute upper respiratory tract infection, tiotropium improved capsaicin cough reflex sensitivity without a significant correlation

between changes in cough reflex sensitivity and those in pulmonary function.²² In previous and recent studies conducted on healthy subjects and patients with asthma, bronchodilation did not affect cough reflex sensitivity.^{28,46,47} Therefore, we think that bronchodilator effect of tiotropium would not influence cough reflex sensitivity.

There are some limitations of the present study. First, we did not have data regarding bronchodilator response, because our patients did not undergo the bronchodilator reversibility test using short-acting β_2 agonist inhalation before the study enrollment. According to a previous study,⁴⁸ a positive response to albuterol was a predictor of improved airway obstruction by tiotropium, but not asthma control in patients with asthma. These findings suggest that responsiveness to short-acting β_2 agonists may not predict improved asthma control by tiotropium including chronic cough. However, predictive factors of the efficacy of tiotropium in chronic asthmatic cough refractory to ICS/LABA should be clarified in future studies. Second, increased doses of ICS or ICS/LABA might have been effective against persistent cough. Although our patients had already received an ICS dose of 651 ± 189 $\mu\text{g/d}$ before the study enrollment, it might not have been high enough for our patients. In fact, 82% of patients were considered poorly controlled at baseline as evident from the ACT scores. However, most of the patients were stable for asthma symptoms other than persistent cough. Changes in ACT scores, as the secondary outcome of the

present study, were significantly correlated with those in subjective cough measures, suggesting that tiotropium may improve asthma control by ameliorating persistent cough. To address this, however, controlled trials comparing the efficacy of increased doses of ICS or ICS/LABA versus the addition of tiotropium for treating chronic asthmatic cough refractory to ICS/LABA are necessary. Finally, this small cohort study included only 17 patients. Although these results are preliminary, this is the first report to demonstrate the efficacy of tiotropium in chronic asthmatic cough refractory to ICS/LABA. Larger randomized prospective studies with control arms will be needed to confirm these results.

CONCLUSIONS

Chronic asthmatic cough refractory to ICS/LABA is often difficult to treat. Tiotropium may be preferable to other controllers such as leukotriene receptor antagonists and theophylline as add-on medication in such cases. This is the first report to show that tiotropium may ameliorate chronic asthmatic cough by modulating capsaicin cough reflex sensitivity, possibly providing a new therapeutic option for treating refractory cough in patients with asthma.

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ONLINE REPOSITORY

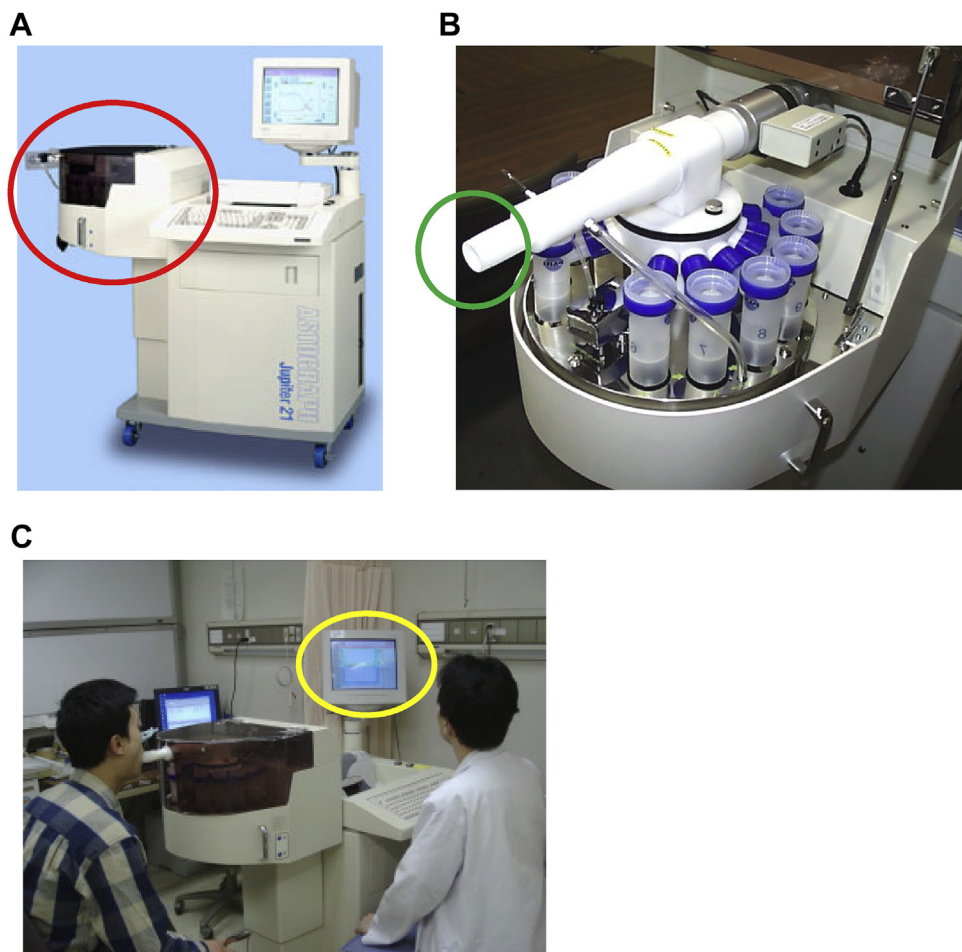


FIGURE E1. Images of Astograph. **(A)** The whole appearance of Astograph. The red circle shows the nebulizer head. **(B)** The contents of the nebulizer head. It includes 12 nebulizers, containing saline, 10 doubling methacholine concentrations, and short-acting β_2 agonists. The green circle shows the mouthpiece port. **(C)** Measurement of airway hyperresponsiveness in a patient. While the patient holds a mouthpiece in his mouth that delivers aerosols from the nebulizer, respiratory resistance can be measured simultaneously and continuously. The examiner watches and checks the monitor (the yellow circle).

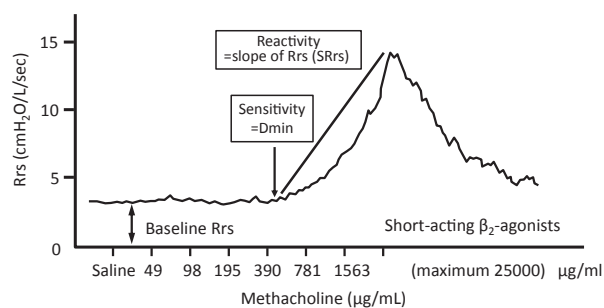


FIGURE E2. Dose-response curve in the measurement of airway hyperresponsiveness using Astograph. On the monitor of Astograph, the dose-response curve is presented in real-time fashion. D_{min} is used as the airway sensitivity index. The slope of the methacholine Rrs dose-response curve is used to measure airway reactivity. Methacholine can be switched to short-acting β_2 agonists as soon as the Rrs reaches twice the baseline value. D_{min} , Cumulative dose of inhaled methacholine at the inflection point that Rrs begins to increase; Rrs, respiratory resistance.