# Bronchodilator-Resistive Cough in Atopic Patients: Bronchial Reversibility and Hyperresponsiveness

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**The number of atopic patients presenting only chronic non-productive cough appears to be increasing. This study was conducted to confirm the existence of non-asthmatic cough associated with atopy. We prospectively examined atopic findings, therapeutic effects of inhaled procaterol, azelastin, and/or glucocorticoids, improvement of $FEV_1$ by bronchodilator therapy and bronchial responsiveness to methacholine in 20 patients. The cough was relieved by inhaled procaterol in 10 patients (Group 2) but not in the other 10 patients (Group 1). The increase in $FEV_1$ by inhaled salbutamol following aminophylline injection was significantly less in Group 1 than in Group 2. Bronchial responsiveness to methacholine was normal in Group 1 while that in Group 2 was hyperreactive. These findings indicate that there is atopic non-asthmatic bronchodilator-resistive cough (Group 1) which is a different entity from bronchodilator-responsive cough (Group 2), or the so-called "cough variant asthma".**
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*Key words:* chronic non-productive cough, atopy, bronchodilator therapy, bronchial reversibility, bronchial hyperresponsiveness

## Introduction

Cough is a common presenting symptom in general practice and in the chest clinic. Patients presenting with non-productive cough resistant to antibiotics and the usual antitussive agents are frequently introduced to our clinic for diagnosis and treatment. It has been established that cough can be the sole manifestation of asthma, cough variant asthma with bronchial hyperresponsiveness (1, 2), a feature of bronchial asthma (3). In these cases, bronchodilators effectively relieve the cough (1, 2). On the other hand, some patients have a bronchodilator-resistive non-productive cough associated with atopy which is diminished by selective potent histamine H1-receptor antagonists and/or glucocorticosteroids.

Salem and Aviado in 1964 (4) proposed that, rather than the cough stimulus interacting directly with cough receptors, cough receptors may be stimulated by local bronchoconstriction. However, there are some findings that cough occurs independent of bronchoconstriction (5–7). In this study we examined prospectively 1) chronic non-productive cough associated with atopy with respect to 2) the effect of inhaled procaterol which is a selective $\beta_2$-adrenergic stimulant, bronchial responsiveness to methacholine, and 3) the bronchodilating effect of intravenously administered aminophylline plus inhaled salbutamol. The results indicated that atopic non-asthmatic bronchodilator-resistive cough which presents with almost normal bronchial responsiveness is different from bronchodilator-responsive cough which is considered to be cough variant asthma (1, 2).

## Patients and Methods

Twenty patients presenting with only non-productive cough for more than 2 months received procaterol inhalation therapy for at least 1 week, a bronchial reversibility test involving the inhalation of salbutamol following the intravenous injection of aminophylline and a methacholine provocation test. In all of the patients, the cough resolved completely on procaterol inhalation therapy, oral administration of azelastin and/or corticosteroid therapy. Neither respiratory disease nor postnasal drip could be identified to account for their symptoms. All 20 patients were non-smokers. Sputum could be obtained from only 5 of the patients, who had

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minimal sputum production in the morning; the other 15 had no expectoration. The sputum examinations revealed no causative organism such as bacteria or mycobacterium tuberculosis but did reveal eosinophils in 3 of the 5 patients. All patients had one or more of the following atopic findings: past history and/or complication of allergic diseases except for bronchial asthma, family history of allergic diseases, peripheral blood eosinophilia, elevated total IgE level in serum, positive specific IgE antibody to common inhalants or positive allergen skin test. Forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and $FEV_1$/FVC ratio were within normal limits. Bronchial reversibility test was performed at the first visit. Spirometry was taken before and 30 minutes after inhalation of 2.5 mg of salbutamol following the intravenous administration of aminophylline (250 mg). Then, all the patients were given 20 $\mu$g of procaterol aerosol through a metered dose inhaler regularly 4 times a day and freely during a cough attack in the first week. When the therapy was not effective, they were given 2 mg of azelastin twice daily during the second week. When the cough was not relieved by the treatments, aerosol or oral steroid therapy was started. The symptoms were relieved completely in all of the patients. The response to each drug was characterized as one of following: excellent (complete relief of cough), good (relief of cough with a remaining mild cough), fairly good (decreased severity of cough attack), poor (no effect on cough attack). At the second or third visit before steroid therapy, a methacholine provocation test (8) was performed. Methacholine chloride was dissolved in physiological saline to make solutions of 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20, 40, 80 or 160 mg/ml. Saline and methacholine were inhaled from a Devilbiss 646 nebulizer (Devilbiss Co., Somerset, PA, USA) operated by compressed air at 5 l/min. The nebulizer output was 0.28 ml/2 min. Saline was inhaled first for two minutes and the $FEV_1$ was measured on a dry wedge spirometer (Transfer test, P.K. Morgan Ltd., UK). Since the change in $FEV_1$ from the baseline after the inhalation of saline was 10% or less in all subjects, inhalation of methacholine was also started. Methacholine was inhaled for two minutes by tidal breathing wearing a nose clip, and this was followed immediately by spirometry. Increasing concentrations were inhaled until a fall of 20% or more in $FEV_1$ occurred. The measured values were plotted on semilogarithmic graph paper and the methacholine provocative concentration producing a 20% fall in $FEV_1$ ($PC_{20}$-$FEV_1$) was calculated.

Methacholine $PC_{20}$-$FEV_1$ values were expressed as geometric means with the geometric standard error of the mean (GSEM) expressed as a factor. Values for baseline FVC and $FEV_1$ were reported as arithmetic means and standard errors of the mean (SEM).

Table 1. Profile of Patients with Chronic Non-productive Cough

| Case No | Sex | Age (years) | Duration of cough (months) | Sputum | Tickle in throat | History of wheezing | Expiratory rhonchi: Deep breath | Expiratory rhonchi: Forced expiration | Time of cough attack | Inducers of cough |
|---|---|---|---|---|---|---|---|---|---|---|
| Bronchodilator-resistive cough | | | | | | | | | | |
| 1 | F | 54 | 4 | − | + | − | − | − | Bedtime, early morning | − |
| 2 | F | 41 | 3 | − | + | − | − | − | Evening, rising | − |
| 3 | F | 33 | 2 | − | + | − | − | − | Bedtime, evening | − |
| 4 | F | 60 | 6 | − | + | − | − | − | Midnight to morning | Dust, passive smoking |
| 5 | F | 52 | 4 | minimal | + | − | − | − | Rising | Cool air, passive smoking |
| 6 | F | 52 | 2 | − | + | − | − | − | Bedtime, midnight to morning | Alcohol, speaking |
| 7 | F | 39 | 4 | minimal | + | − | − | − | Bedtime, midnight to morning | Cool air |
| 8 | F | 33 | 2 | − | + | − | − | + | Rising | Passive smoking, speaking |
| 9 | M | 75 | 3 | − | + | − | − | − | All day and night | Exercise |
| 10 | F | 32 | 5 | − | + | − | − | − | Bedtime | Speaking, cool air Passive smoking |
| Bronchodilator-responsive cough | | | | | | | | | | |
| 11 | F | 59 | 4 | − | + | − | − | − | Bedtime, early morning | Speaking, exercise |
| 12 | F | 52 | 36 | − | − | + | − | − | Midnight to morning | Speaking, cool air |
| 13 | F | 59 | 2 | minimal | + | + | − | − | Bedtime | − |
| 14 | F | 37 | 1 | − | − | + | + | + | Bedtime, midnight to morning | − |
| 15 | F | 31 | 4 | − | + | + | − | − | Midnight to morning | − |
| 16 | F | 59 | 5 | − | + | − | − | + | Early morning | Cool air |
| 17 | F | 56 | 2 | minimal | + | + | − | − | Bedtime | Speaking, exercise |
| 18 | F | 62 | 3 | minimal | + | + | − | + | Early morning | − |
| 19 | F | 27 | 30 | − | − | − | − | + | Bedtime | Exercise, cool air, alcohol |
| 20 | M | 59 | 6 | − | + | − | − | + | Bedtime | − |

## Results

Ten patients (Case No 1–10) had bronchodilator-resistive cough which was not relieved by the inhalation of procaterol (20 $\mu$g, 4 times a day for 1 week) (Group 1). The other 10 patients (Case No 11–20) had bronchodilator-responsive cough which was relieved by the procaterol inhalation therapy (Group 2). The clinical profiles of the patients are shown in Table 1. In both groups most of the patients were women (9 of 10 in both Group 1 and Group 2). Non-productive cough was associated with a "tickle" in the throat in all patients (100%) in Group 1 and in 7 patients (70%) in Group 2. Six patients (60%) had a history of wheeze in Group 2 but none had this history in Group 1. As shown in Table 1, the time of the cough attack was characteristically at bedtime, between midnight and morning, in the early morning and/or at rising in most of the patients. The cough was usually induced by passive smoking, cool air, exercise, alcohol and/or speaking.

Effects of inhaled procaterol and azelastin on the coughs and successful treatments are summarized in Table 2. The effect of azelastin was excellent in 7, good in 2, and poor in only 1 patient in Group 1. On the other hand, azelastin was excellent in 4, good in 1, fairly good in 1 and poor in 1 patient in Group 2. In Group 1, azelastin was successful in 8 patients and steroid therapy (15 mg/day of prednisolone) was necessary to abolish the cough completely in the remaining 2 patients. In Group 2, treatment was successful with azelastin in 1, procaterol inhalation in 2, theophylline in 1, beclomethasone inhalation in 2, a combination of azelastin and procaterol in 3 and a combination of procaterol and beclomethasone in 1 patient.

Table 2. Therapeutic Results for Chronic Non-Productive Cough

| Case No | Inhalation of procaterol | Azelastin | Successful treatment |
|---|---|---|---|
| Bronchodilator-resistive cough | | | |
| 1 | − | ++ | Azelastin |
| 2 | − | +++ | Azelastin |
| 3 | − | +++ | Azelastin |
| 4 | − | +++ | Azelastin |
| 5 | − | +++ | Azelastin |
| 6 | − | +++ | Azelastin |
| 7 | + | +++ | Azelastin |
| 8 | − | +++ | Azelastin |
| 9 | − | − | Prednisolone |
| 10 | − | ++ | Prednisolone |
| Bronchodilator-responsive cough | | | |
| 11 | +++ | +++ | Azelastin |
| 12 | ++ | ++ | BDI |
| 13 | +++ | +++ | Procaterol+Azelastin |
| 14 | +++ | − | BDI |
| 15 | +++ | NT | Procaterol |
| 16 | +++ | NT | Procaterol+BDI |
| 17 | +++ | +++ | Procaterol |
| 18 | ++ | + | Procaterol+Azelastin |
| 19 | +++ | +++ | Procaterol+Azelastin |
| 20 | +++ | NT | Theophylline |

+++ Excellent, ++ Good, + Fairly good, − Poor.
BDI: Beclomethasone dipropionate, NT: Not tested

Characteristics of atopic tendency are listed in Table 3. All patients had one or more of the following atopic tendencies: past history of allergic diseases, complication of allergic diseases except for asthma, family history of allergic diseases, peripheral blood eosinophilia, elevated total serum IgE level, positive specific IgE antibody or positive allergen skin test.

Baseline pulmonary function, bronchodilator response and bronchial responsiveness to methacholine are shown in Table 4. Forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC) and $FEV_1$/FVC ratio were within normal limits in all patients except for Case 20. These values did not differ between Group 1 and Group 2. The increase in $FEV_1$ induced by bronchodilator therapy (salbutamol inhalation following aminophylline injection) in Group 1 was $0.05 \pm 0.03$ (mean ± SE) l which was significantly ($p < 0.01$) less than the value in Group 2, $0.20 \pm 0.04$ l. The percent increase in $FEV_1$ after the therapy was $1.8 \pm 1.2\%$ in Group 1, which was significantly ($p < 0.02$) less than that in Group 2, $9.0 \pm 2.5\%$. The geometric mean value of $PC_{20}$-$FEV_1$ in Group 1 was 15.1 (GSEM, 1.58) mg/ml, which was significantly ($p < 0.01$) greater than that in Group 2, 2.63 (GSEM, 1.45) mg/ml (Fig. 1).

Figure 2 shows the relationship between increases in the $FEV_1$ induced by bronchodilator therapy and the logarithmic value of $PC_{20}$-$FEV_1$ in both Groups. There was significant correlation ($y = -2.40x + 1.10$, $r = -0.47$, $p < 0.05$) between the increases in the $FEV_1$ induced by bronchodilator therapy and the $PC_{20}$-$FEV_1$.

## Discussion

In an editorial (9) which discusses whether cough and wheeze in asthma are interdependent, it is suggested that cough and wheeze in asthma may be produced by different mediators. Fuller and Jackson described in an editorial (10) that it is unclear whether inhaled bronchodilators are effective in patients with cough in the absence of airflow obstruction. On the other hand, it is established that a non-productive cough can be the sole manifestation in some patients with the so called "cough variant asthma" who have bronchial hyperresponsiveness (1, 2). In such cases, bronchodilators such as $\beta_2$-adrenergic stimulants and theophylline have been shown to be effective in relieving the cough (1, 2). However, we have had practical experience with a bronchodilator-resistive cough in atopic non-smokers, who were introduced to our clinic because their cough was resistant to antibiotics, common antitussive drugs and oral bronchodilators. There were 66 such patients (18

Table 3. Characteristics of Atopic Tendency

| Case No | Allergic diseases: Past history | Complication | Family history | Eosinophils in peripheral blood (%) | (/μl) | Eosinophils in sputum | Total IgE in serum (IU/ml) | Specific IgE in serum | Allergen skin test |
|---|---|---|---|---|---|---|---|---|---|
| Bronchodilator-resistive cough | | | | | | | | | |
| 1 | AR | AR | UR | 7 | 427 | NT | 57 | – | – |
| 2 | – | – | AR | 1 | 75 | NT | 12 | – | HD, JC |
| 3 | UR | UR | AR, UR | 2 | 112 | NT | 36 | – | – |
| 4 | UR | – | – | 5 | 375 | NT | 1,595 | – | – |
| 5 | UR, AR | UR, AR | AR | 6 | 360 | +++ | 35 | – | – |
| 6 | – | – | BA, UR | 2 | 78 | NT | 12 | – | NT |
| 7 | – | – | UR | 4 | 332 | – | 26 | NT | NT |
| 8 | – | – | BA, AR, AD | 2 | 74 | NT | 44 | – | – |
| 9 | UR | UR | – | 4 | 348 | NT | 1,374 | Asp | NT |
| 10 | AR | – | BA | 6 | 414 | NT | 264 | ND, D | HD |
| Bronchodilator-responsive cough | | | | | | | | | |
| 11 | UR | AR | – | 11 | 605 | NT | 171 | – | – |
| 12 | – | AR | – | 8 | 624 | NT | 33 | – | – |
| 13 | UR | UR | – | 10 | 670 | ++ | 29 | – | – |
| 14 | AR | AR | BA, AR | 5 | 175 | NT | 167 | JC, RW | NT |
| 15 | AR | AR | – | 8 | 512 | NT | 602 | D, JC | HD, JC |
| 16 | AR | AR | AR | 6 | 480 | NT | 296 | D, HD | HD |
| 17 | AR, AD | AR | – | 6 | 312 | +++ | 85 | – | – |
| 18 | AR | AR | – | 7 | 678 | – | 69 | JC | NT |
| 19 | AR, UR | AR, UR | BA | 20 | 1,460 | NT | 53 | HD | HD |
| 20 | AR | AR | – | 7 | 504 | NT | 1,779 | D, HD | NT |

NT: not tested, AR: allergic rhinitis, UR: urticaria, AD: atopic dermatitis, BA: bronchial asthma, HD: house dust, JC: Japanese cedar, D: dermatophagoides, RW: ragweed.

Table 4. Baseline pulmonary function, bronchodilator response and bronchial responsiveness

| Case No | FVC (l) | FVC (% pred) | $FEV_1$ (l) | $FEV_1$ (% pred) | $FEV_1$/FVC (%) | Response to bronchodilators: $\Delta FEV_1$ (l) | $\Delta FEV_1$ (%) | $PC_{20}$-$FEV_1$ (mg/ml) |
|---|---|---|---|---|---|---|---|---|
| Bronchodilator-resistive cough | | | | | | | | |
| 1 | 2.64 | 107 | 2.29 | 115 | 87 | 0.02 | 0.9 | 17.3 |
| 2 | 3.53 | 123 | 2.74 | 101 | 78 | 0.05 | 1.8 | 160 |
| 3 | 3.06 | 103 | 2.48 | 87 | 81 | 0.00 | 0.0 | 4.83 |
| 4 | 2.75 | 118 | 2.27 | 131 | 83 | 0.01 | 0.4 | 4.11 |
| 5 | 2.65 | 108 | 2.11 | 108 | 80 | NT | NT | 40.6 |
| 6 | 3.20 | 129 | 2.32 | 112 | 73 | 0.16 | 6.9 | NT |
| 7 | 2.82 | 102 | 2.30 | 91 | 82 | NT | NT | 6.60 |
| 8 | 3.09 | 110 | 2.49 | 94 | 81 | 0.12 | 4.8 | 12.6 |
| 9 | 2.75 | 92 | 2.08 | 110 | 76 | −0.08 | −3.8 | 80 |
| 10 | 3.68 | 120 | 3.27 | 105 | 89 | 0.11 | 3.4 | 2.28 |
| Bronchodilator-responsive cough | | | | | | | | |
| 11 | 3.66 | 144 | 2.65 | 122 | 72 | 0.16 | 6.0 | 9.58 |
| 12 | 3.42 | 123 | 2.44 | 103 | 71 | 0.15 | 6.1 | 0.44 |
| 13 | 1.84 | 81 | 1.48 | 88 | 80 | 0.08 | 5.3 | 20.0 |
| 14 | 2.74 | 99 | 2.28 | 89 | 83 | 0.48 | 26.1 | 2.50 |
| 15 | 3.28 | 113 | 2.52 | 91 | 77 | 0.24 | 9.5 | 2.00 |
| 16 | 2.88 | 119 | 2.36 | 124 | 82 | 0.11 | 2.3 | 1.25 |
| 17 | 3.14 | 123 | 2.47 | 115 | 79 | 0.29 | 11.9 | 1.35 |
| 18 | 2.64 | 117 | 2.12 | 137 | 80 | NT | NT | 6.93 |
| 19 | 3.39 | 108 | 2.96 | 93 | 87 | 0.06 | 2.0 | 0.80 |
| 20 | 2.48 | 74 | 1.96 | 77 | 79 | 0.24 | 12.2 | 3.97 |
| Difference | NS | NS | NS | NS | NS | $P<0.01$ | $P<0.02$ | $P<0.01$ |

Difference: Bronchodilator-resistive cough vs bronchodilator-responsive cough.

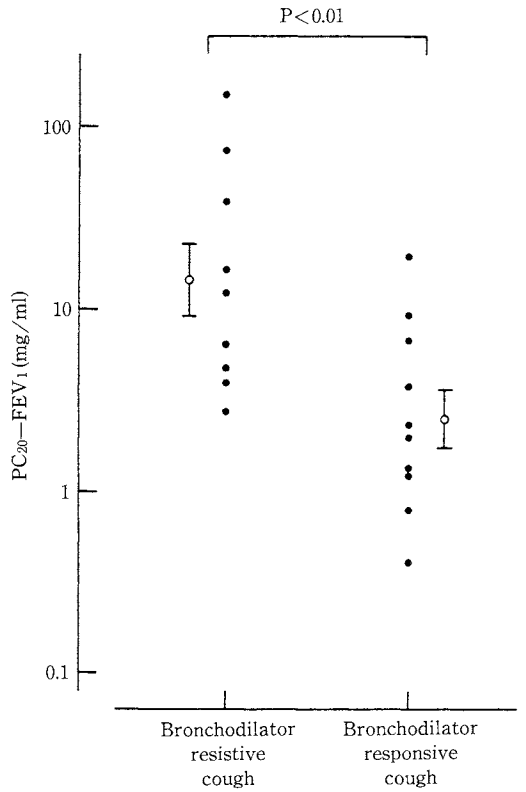


Fig. 1. Bronchial responsiveness to methacholine in patients with chronic non-productive cough. $PC_{20}$-$FEV_1$, provocative concentration of methacholine which produces a 20% fall in forced expiratory volume in 1 second.

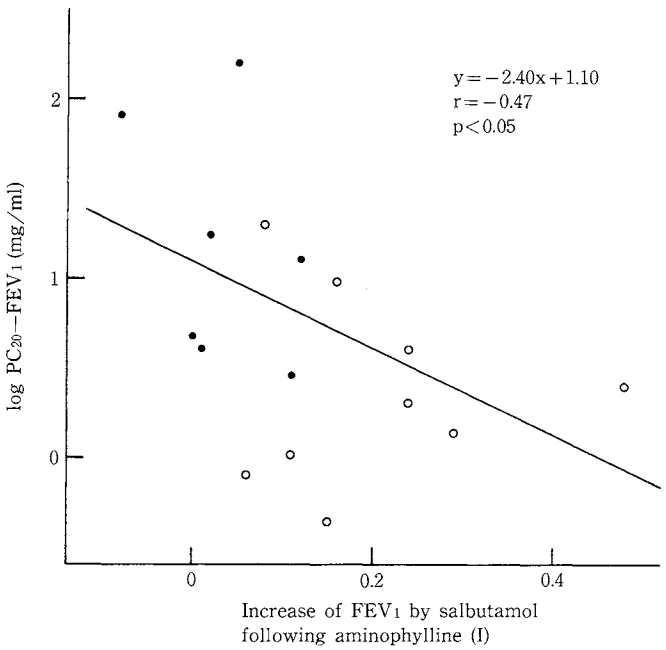


Fig. 2. Relationship between the increase in $FEV_1$ induced by inhaled salbutamol following aminophylline injection and logarithm of $PC_{20}$-$FEV_1$ in patients with bronchodilator-resistive cough (•) and bronchodilator-responsive cough (○).

males and 48 females) who visited our chest and allergy clinic from July 1, 1988 to June 30, 1990. The cough of all patients was relieved completely by azelastin and/or corticosteroid therapy. The bronchial responsiveness of these patients to methacholine was equal to that of atopic subjects without respiratory symptoms (11). This prospective study was conducted to ensure that atopic bronchodilator-resistive cough is a distinct entity from bronchodilator-responsive cough (cough variant asthma) (1, 2).

As this study was an open but not double-blinded cross-over study, one may claim that the antitussive effect of inhaled procaterol was not adequately evaluated. However, when bronchodilator-resistive cough and bronchodilator-responsive cough were defined according to the efficacy of the procaterol treatment, bronchial responsiveness to methacholine and bronchial reversibility differed significantly between the two types of cough. Namely, bronchial responsiveness to methacholine and the effect of bronchodilator therapy were significantly greater in bronchodilator-responsive cough. In addition, there was a significant correlation between bronchial responsiveness and bronchodilator response in all patients. There are some findings that cough receptors are functionally different from irritant receptors and also that cough occurs independently of bronchoconstriction (5−7). It is thought that cough and bronchoconstrictor reflexes are closely related and may potentiate one another, but neither is entirely dependent on the other for its action (9). The results of this study support this thought. Although bronchodilators have been shown to relieve the low chloride ion-induced cough (12), it has been reported that they relieve citric acid-induced cough in asthmatic patients but not in normal subjects (13). We also found in an earlier study that neither inhaled procaterol nor inhaled ipratropium bromide, an anticholinergic agent, relieves cough which is induced by tartaric acid or capsaicin in normal volunteers (14).

It is well-known that angiotensin-converting enzyme inhibitors induce non-productive cough more frequently in women than in men (15). In this study, females were predominant with respect to bronchodilator-resistive cough and bronchodilator-responsive cough. Since we had been interested in the sex-specific difference in cough incidence, we measured the cough threshold to inhaled tartaric acid in normal men and women and found that cough receptors are more sensitive in women than in men (16). We hypothesize, therefore, that cough is induced more easily in women than in men even if cough stimuli are of the same intensity.

In this study, azelastin was shown to be effective against two types of cough. Murray and co-workers (17) reported that antihistamines were effective against the allergic cough syndrome in children, but epinephrine was not. Azelastin is a newly developed $H_1$-receptor antagonist (18, 19), which has been shown to have a

variety of pharmacological activities such as inhibition of the release of mediators of anaphylaxis, non-specific bronchodilation and block of leukotriene-induced bronchoconstriction. From our clinical experience, azelastin and terfenadin as more potent $H_1$-blockers are more effective against cough than clemastin, a classical antihistamine. Because it has been recognized that $H_1$-blockers have an antitussive effect on post-nasal drip-induced cough (20), it may be claimed that post-nasal drip is responsible for bronchodilator-resistive cough. But ongoing allergic rhinitis was complicated in only two out of 10 patients with bronchodilator-resistive cough. Furthermore, the cough preceded nasal symptoms in one patient and the nasal symptoms had become rather mild in the other. Consequently, we do not believe that the antitussive effect of azelastin is secondary to its effect against post-nasal drip. Recently it was shown that azelastin inhibits the release of substance-P from C-fiber endings which is induced by electrical stimulation (21) and substance-P is considered to be a tussive neuropeptide. This mechanism may be responsible in part for the antitussive effect of azelastin. Although we do not know if the effect of azelastin on cough results from its blocking $H_1$-receptors and/or substance-P release from C-fiber endings, this is the first report on the effect of selective $H_1$-blockers on atopic bronchodilator-resistive cough. Atopic bronchodilator-resistive cough may resemble eosinophilic bronchitis without asthma which is responsive to corticosteroid therapy (22). In this study, sputum could be obtained from only 2 out of 10 patients with bronchodilator-resistive cough for a study of eosinophils. In only one of the 2 patients, however, was sputum eosinophilia documented.

Finally, this clinical study demonstrated that atopic non-asthmatic bronchodilator-resistive cough differs from bronchodilator-responsive "cough variant asthma" and that azelastin is effective against this cough. Further studies, however, are needed to clarify the mechanism underlying azelastin's inhibition of non-asthmatic bronchodilator-resistive cough.

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