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Cough Sensitivity and Extrathoracic Airway Responsiveness to Inhaled Capsaicin in Chronic Cough Patients

Enhanced cough response has been frequently observed in chronic cough. Recently, extrathoracic airway constriction to inhaled histamine was demonstrated in some chronic cough patients. However, relation between extrathoracic airway hyperresponsiveness (EAHR) and cough sensitivity determined by capsaicin inhalation is unclear in each etiological entity of chronic cough. Seventy-seven patients, with dry cough persisting for 3 or more weeks, normal spirometry and chest radiography, and 15 controls, underwent methacholine bronchial provocation test and capsaicin cough provocation test. Elicited cough number and flow-volume curve was examined after inhalation of capsaicin to evaluate cough sensitivity and EAHR. Thirty-three patients, with postnasal drip, showed normal extrathoracic airway responsiveness, and 27 of them showed normal cough sensitivity to capsaicin. Cough sensitivity was enhanced in 14 patients with cough variant asthma (CVA) who showed bronchial hyperresponsiveness; EAHR to inhaled capsaicin was present in 12 of them. The remaining 30 patients were tentatively diagnosed as idiopathic chronic cough (ICC). Eleven ICC patients showed enhanced cough sensitivity and EAHR to inhaled capsaicin while 19 patients showed normal values. These results indicate that cough sensitivity is closely related with extrathoracic airway responsiveness during capsaicin provocation in some chronic cough patients. EAHR and enhanced cough sensitivity to inhaled capsaicin may be a part of mechanism developing chronic cough.

Key Words : *Cough; Hypersensitivity; Airway Obstruction; Capsaicin*

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INTRODUCTION

Chronic cough, usually defined as cough persisting for 3 weeks or longer, is sometimes a vexing medical problem. The prevalence of chronic cough among nonsmoking adults is reported to range from 14 to 23% (1, 2). The most common causes of chronic cough are postnasal drip (PND), asthma, gastroesophageal reflux (GER), and drugs such as angiotensin converting enzyme inhibitors (ACEI) (3).

However, the etiological diagnosis is not easy in some patients especially if the obvious clues are not present in symptoms, radiography, or spirometry. In some cases, a specific cause of cough cannot be identified despite thorough investigation. There is no consensus about the management of not only idiopathic chronic cough (ICC) but also chronic cough refractory to specific treatment or recurring after stopping medication. We presume that identification of the mechanisms of chronic cough would permit the development of successful treatment modalities.

Bronchial hyperresponsiveness (BHR) (4), eosinophilic bronchial inflammation (5), or abnormal bronchial intraepithelial nerve (6) have been observed in some patients with chronic cough. Enhanced cough sensitivity, which is independent of BHR, was reported in chronic cough due to GER and ACEI- induced cough (7), cough after upper respiratory infection (URI) (8), and ICC (7, 9). This enhanced cough reflex triggered by various chemical and mechanical factors has been regarded as a common and central pathophysiology of chronic cough by many researchers (4, 7-10). With all of those results, however, the exact mechanism of chronic cough has not been clarified.

Because cough receptors are predominant along the pharyngolaryngeal area (11), abnormalities in this extrathoracic airway might be important in the pathogenetic mechanism of chronic cough. Recently, extrathoracic airway hyperresponsiveness (EAHR) during histamine inhalation was observed in the patients with asthma-like symptoms (12), GER (13), and ACEI-induced cough (14). We hypothesized that sensory hypersensitivity of extrathoracic airway characterized by increased cough sensitivity and EAHR might induce chronic cough especially in the subjects not to have any definite clues suggesting abnormalities of lower airway and in the patients

showing inappropriate cough response such as cough variant asthma (CVA).

To the best of our knowledge, there has been no study on the relationship between cough sensitivity and extrathoracic airway responsiveness on capsaicin inhalation, which is the most commonly used method to determine cough sensitivity and is known to stimulate cough receptors effectively without influences on lower airway such as bronchocontriction. In this study, we investigated cough sensitivity and extrathoracic airway responsiveness to inhaled capsaicin in chronic cough of diverse causes to characterize the underlying pathophysiology.

MATERIALS AND METHODS

Subjects

Patients complaining chronic dry cough lasting 3 or more weeks, who did not have symptoms of dyspnea or purulent sputum, were recruited from the outpatient department of our institution. All of the patients were nonsmokers, had normal chest radiographs, normal spirometry [both forced expiratory volume for 1 sec (FEV1) and forced vital capacity: (FVC) >80% of predicted values], and did not have upper respiratory tract infection in the preceding 2 months. No patients have taken antihypertensive medications such as ACEIs and beta-blockers. Exclusion criteria was other chronic or systemic illness, pregnancy, and intake of any medication within 1 week before the study. Controls were 15 normal nonsmoking healthy volunteers.

Methacholine bronchial provocation test

Methacholine bronchial provocation was performed by use of a dosimeter-controlled jet nebulizer with increasing doses of methacholine from 0.625 to 25 mg/mL. Each dose of methacholine was inhaled by 5 slow and vital capacity breaths. At one and 3 min after each set of inhalation, spirometry was recorded. The interval between one dose and the next was 5 min. The concentration causing a 20% fall in FEV1 from baseline (PC_{20}) was used as the threshold of bronchial responsiveness and BHR was defined when PC_{20} was less than 25 mg/dL.

Capsaicin cough provocation test and determination of cough sensitivity and extrathoracic airway responsiveness

Subjects inhaled a single breath of saline and doubling concentrations of capsaicin (Sigma, St. Louis, Mo, U.S.A.) ranging from 0.5 to 250 μM/L at about 1.5-min intervals. Each inhalation was controlled by the use of a dosimeter and jet nebulizer. The number of cough in response to each concentration of capsaicin was counted by the investigator during and 30 sec after inhalation and recording of flow-volume loop was performed after each inhalation.

In the control group, the lowest concentration of capsaicin that elicited at least 5 consecutive coughs (C_5) was over 64 μM/L in all subjects. Based on these results, enhanced cough sensitivity was defined when C_5 was less than 64 μM/L.

With regard to extrathoracic airway responsiveness, the capsaicin concentration causing a 20% fall in peak inspiratory flow (PIF) from baseline (PC_{20PIF}) was used as a threshold of extrathoracic airway constriction. Capsaicin inhalation was continued until 20% fall of PIF occurred or capsaicin concentration reached to 250 μM/L. In addition, the flow-volume curve was carefully observed to detect a pattern of variable extrathoracic airway obstruction that showed a reduced PIF, a flattened configuration of the mid-portion of the inspiratory flow-volume curve, and absence of significant change in pulmonary function in the expiratory phase.

Control subjects never showed any significant extrathoracic airway narrowing up to 250 μM/L of capsaicin concentration. According to the results from control subjects, EAHR was arbitrarily defined when PC_{20PIF} was less than 250 μM/L and a pattern of variable extrathoracic airway obstruction was induced simultaneously.

Statistical analysis

The data are presented as mean±standard deviation. Comparisons of data between groups were made by chi-square test and Kruskal Wallis test. Correlations were calculated using Pearson's correlation test. A p-value <0.05 was considered significant.

RESULTS

Causative disorders of chronic cough

The patients with PND-associated cough were classified by absence of BHR to inhaled methacholine and having one or more of the following criteria; any symptoms suggesting PND such as throat discomfort, radiological evidence such as the findings of opacity, air-fluid level, or mucoperiosteal thickening of paranasal sinuses, and good response to antihistamines and decongestants for 2 weeks (symptom scores after treatment decreased to less than 50% than before treatment measured by visual analogue scale). CVA was defined by the presence of BHR to inhaled methacholine and absence of any evidence of other diseases. Diagnostic criteria of GER were clinical histories such as inducing cough at supine position, having epigastric soreness, reflux symptoms or past medical history of peptic ulcers, and response to treatment to 2 weeks' therapeutic trial with H_2 blocker. However, there was no patient definitely diagnosed as having a GER associated cough. The remaining patients with persistent unexplained

Table 1. Characteristics of chronic cough patients

	PND (n=33)	CVA (n=14)	ICC		Control (n=15)	*p*-value
			ECS (n=11)	NCS (n=19)		
Age (yr)	44.3±14.4	38.0±15.1	51.4±11.3	40.8±14.5	29.4±3.5	<0.01
Sex (M/F)	10/23	6/8	4/7	8/11	5/10	NS
bFEV1(% pred)	104±14	99±8	108±18	104±12	95±12	NS
pcFEV1(% pred)	101±13	95±8	104±13	102±12	92±13	NS
PC_{20} (mg/dL)	>25	4.36±4.5	>25	>25	>25	
ECS/NCS (n)	6/27	14/0	11/0	0/19	0/15	
EAHR (+/-)	0/33	12/2	11/0	0/19	0/15	

PND, postnasal drip; CVA, cough variant asthma; ICC, idiopathic chronic cough; ECS, enhanced cough sensitivity; NCS, normal cough sensitivity; bFEV1, baseline FEV1; pcFEV1, FEV1 after capsaicin provocation test; % pred, percent of predicted value; PC_{20}, methacholine provocation concentration causing 20% fall of FEV1 (mg/dL); EAHR, extrathoracic airway hyperresponsiveness; NS, not significant.

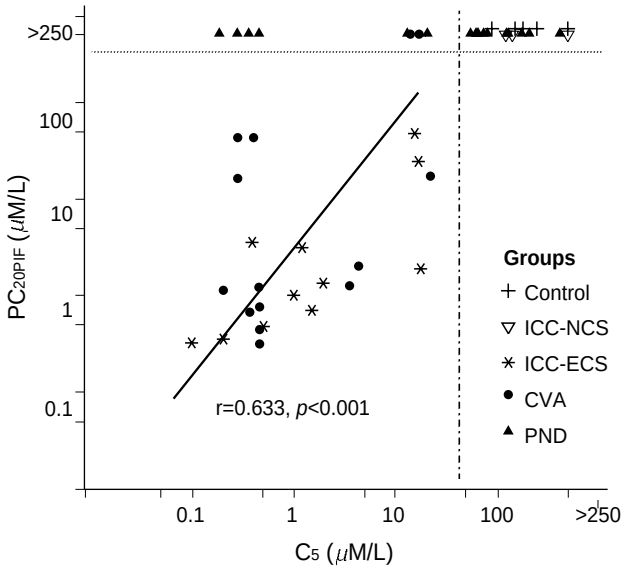

Fig. 1. Distribution of cough sensitivity and extrathoracic airway responsiveness to inhaled capsaicin in chronic cough patients of various causes. PND, patients with postnasal drip; CVA, patients with cough variant asthma; ICC-ECS, patients with idiopathic chronic cough showing enhanced cough sensitivity; ICC-NCS, patients with idiopathic chronic cough showing normal cough sensitivity; PC_{20PIF}, capsaicin provocation concentration causing 20% fall of peak inspiratory flow; C_5, lowest capsaicin concentration inducing at least 5 coughs; area below horizontal line, presence of extrathoracic airway hyperresponsiveness to inhaled capsaicin; area left sided from vertical line, enhanced cough sensitivity to inhaled capsaicin.

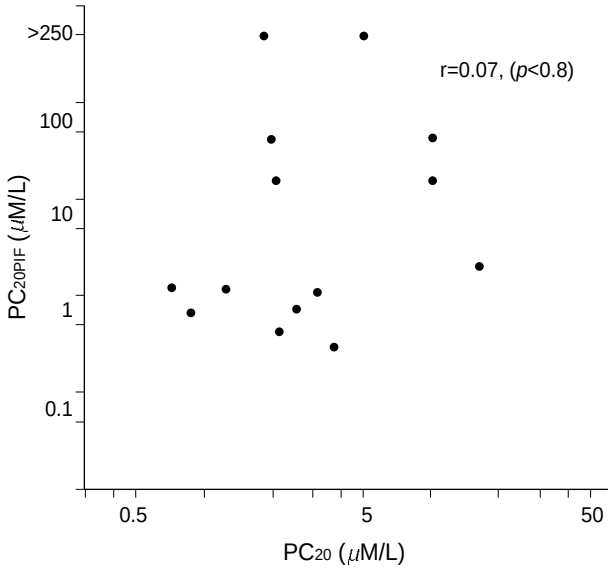

Fig. 2. Relationship between bronchial responsiveness to inhaled methacholine and extrathoracic airway responsiveness to inhaled capsaicin in patients with cough variant asthma. PC_{20}, methacholine provocation concentration causing 20% fall of forced expiratory volume for 1 sec; PC_{20PIF}, same as in Fig. 1.

cough were classified into ICC tentatively.

PND-associated cough was diagnosed in 33 patients. Fourteen patients showed BHR and were classified into CVA. ICC was diagnosed in 30 patients. The airway characteristics of patients and control subjects are summarized in Table 1.

Cough sensitivity and extrathoracic airway hyperresponsiveness

Six of 33 PND patients showed enhanced cough sensitivity and all 33 patients showed normal EAHR to inhaled capsaicin. Enhanced cough sensitivity was observed in all 14 CVA patients and EAHR was present in 12 thereof. Patients with ICC were divided into two groups in relation to cough sensitivity to inhaled capsaicin, i.e., 11 patients with enhanced cough sensitivity and 19 patients with normal. All ICC patients with enhanced cough sensitivity had EAHR to inhaled capsaicin, but those with normal cough sensitivity did not show EAHR (Table 1, Fig. 1).

Values of C_5 were closely related to PC_{20PIF} in all subjects who showed both enhanced cough sensitivity and EAHR to inhaled capsaicin such as the patients with CVA and some of ICC (r=0.633, p<0.0001). In patients with CVA who showed both EAHR to inhaled capsaicin and BHR to inhaled methacholine, no significant correlation between PC_{20} and PC_{20PIF} (Fig. 2).

After capsaicin cough provocation tests, no subjects showed a significant (>20%) decrease of FEV1.

DISCUSSION

The results of this study demonstrate that EAHR to inhaled capsaicin in some etiological entities of chronic cough such as CVA and ICC was closely related to enhanced cough sensitivity. There was no correlation be-tween extrathoracic airway responsiveness to inhaled capsaicin and bronchial responsiveness to inhaled methacholine. Although it is not clear whether the extrathoracic airway constriction is a direct cause or an epiphenomenon, upper airway sensory hypersensitivity independent of lower airway pathology might be one of important mechanisms inducing cough in some entities of chronic cough.

We have observed that enhanced cough induction and inspiratory upper airway flow limitation occurred simultaneously during capsaicin inhalation in most patients with CVA. A group of ICC patients also showed upper airway sensory hypersensitivity, i.e., enhanced cough sensitivity and EAHR to inhaled capsaicin. Therefore, they should not be considered to have habitual or psychogenic coughs. Chronic cough in PND associated with sinusitis is suggested to be caused by mechanical irritations of cough receptors with normal sensitivity. All these results indicate the variety of cough sensitivity, extrathoracic airway responsiveness, and bronchial responsiveness in chronic cough, which might be managed differently.

Recently, the possibility of upper airway abnormalities in the mechanism of chronic cough has been suggested by Bucca et al. (12), who reported EAHR to inhaled histamine in patients having asthma-like symptoms without BHR. They also demonstrated both EAHR and enhanced cough sensitivity to inhaled histamine in chronic cough induced by GER (13) and ACEI (14). The results of our study further support these findings.

Some investigators argued that EAHR to histamine could not be implicated as a single unifying mechanism of chronic cough (15). However, in their study, many chronic cough patients had both rhinitis and GER, which could represent different cough sensitivity, respectively. In addition, capsaicin used in our study directly stimulates cough receptors, and in contrast to histamine, it does not induce bronchoconstriction in humans (16, 17). Therefore, our method using capsaicin inhalation may be more appropriate for evaluating upper airway abnormalities.

In this study, EAHR and enhanced cough sensitivity to inhaled capsaicin was important and the only abnormal finding in one subtype of ICC patients. This EAHR was related not to BHR but to enhanced cough sensitivity. These results may indicate that upper airway sensory hypersensitivity could be the most important mechanism eliciting cough in this subtype of ICC patients. Chronic cough in ICC patients with normal cough sensitivity could be psychogenic. Therefore, capsaicin test may be useful to differentiate psychogenic cough from pathological ICC. However, further studies are needed to clarify this.

The exact mechanism inducing enhanced cough sensitivity has not yet been elucidated. In eosinophilic bronchitis without asthma as Gibson et al. had defined (5), inhaled corticosteroid could improve the cough and sputum eosinophilia (18) and normalize enhanced cough sensitivity (19). Because we did not perform bronchoscopic biopsy or induced sputum analysis, we could not exclude this entity in our ICC patients representing enhanced cough sensitivity. However, considering that patients with typical asthma have shown normal cough sensitivity (20), it is not reasonable to presume that bronchial eosinophilic inflammation per se would be relevant to enhanced cough sensitivity. Until now, the main site of pathology for the enhanced cough sensitivity could not be determined. In addition, the exact pathogenesis of EAHR is presently unknown although some investigators have reported that the edema and constriction of the pharynx and glottis seen at laryngoscopy after histamine inhalation in patients with EAHR suggest the activation of local reflexes having cough receptors as the afferent pathway and skeletal muscles, glands, and vessels as the efferent pathway (21). Further studies are needed to clarify the definite mechanisms of both ICC and EAHR and their association.

There was no definite group of GER-associated cough in our study. However, considering that 2 weeks' treatment is too short to observe any therapeutic benefit on that, some patients with ICC showing enhanced cough sensitivity might have had GER-associated cough. In that case, the mechanism of GER-associated cough that has not yet been clarified may be associated with upper airway sensory hypersensitivity.

In this study, we measured PIF to test extrathoracic airway responsiveness and a 20% decline in PIF from the baseline value was used as an index to define EAHR to inhaled capsaicin, while the provocation concentration of histamine associated with a 25% fall in the maximal mid-inspiratory flow was used as a criterion of extrathoracic airway narrowing in other studies (12, 14). There was a report that symptoms of extrathoracic airway obstruction such as stridor and dyspnea were significantly improved according to 20-30% increase of PIF in patients with reversible extrathoracic airway obstruction (22). Also, PIF is a very simple method to detect inspiratory flow limitation when a pattern of variable extrathoracic airway obstruction is observed in the flow-volume curve. Therefore, it is considered that PC_{20PIF} could be a convenient and reasonable index to detect EAHR to inhaled capsaicin. We divided our chronic cough patients into the enhanced cough sensitivity group and normal cough sensitivity group on the basis of data from control subjects by using the value of C_5. The PC_{20PIF} and the criterion of determining enhanced cough sensitivity used in this study are totally arbitrary indices and further studies are needed to determine the accuracy and usefulness of these parameters.

There has been a controversy about cough sensitivity in PND. Some investigators have observed normal cough sen-

sitivity in patients with PND (7, 10) while others have reported enhanced cough sensitivity (23). In contrast to the results of our study, Bucca et al. (24) detected EAHR on histamine inhalation in most sinusitis patients. In our study, we have observed normal cough sensitivity and extrathoracic airway responsiveness to inhaled capsaicin in presumed PND-associated cough. The reasons for these discrepancies are largely unknown. While patients having typical symptoms of rhinosinusitis were recruited in Bucca's study, our patients complained chronic dry cough despite having some mild and atypical evidences of PND-associated rhinosinusitis. These different characteristics of patients might have contributed to this discrepancy. However, further studies are needed to clarify it.

In conclusion, there is a close relationship between cough sensitivity and extrathoracic airway responsiveness during capsaicin provocation test. It is suggested that extrathoracic airway sensory hypersensitivity may be one of mechanisms developing some subtypes of chronic cough.

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