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Cough receptor sensitivity and bronchial responsiveness in normal and asthmatic subjects

M. Fujimura*, S. Sakamoto*, Y. Kamio**, T. Matsuda*

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ABSTRACT: We examined whether airway cough receptor sensitivity correlates to nonspecific bronchial responsiveness.

We measured cough threshold, the lowest concentration of inhaled tartaric acid eliciting five or more coughs, and the provocative concentration of methacholine producing a 20% fall in forced expiratory volume in one second ($PC_{20}FEV_1$) in 38 normal and 11 asthmatic subjects. All subjects were nonsmokers.

The geometric mean value of $PC_{20}FEV_1$ was 25.7 mg·ml^{-1} (GSEM1.29) and 0.63 mg·ml^{-1} (GSEM1.29) and the geometric mean value of the cough threshold was 115 mg·ml^{-1} (GSEM1.20) and 95.5 mg·ml^{-1} (GSEM1.35) in normal and asthmatic subjects, respectively. The $PC_{20}FEV_1$ was significantly ($p<0.01$) lower in asthmatics than in normals but the cough threshold did not differ between them. No significant correlation was observed between the cough threshold and the $PC_{20}FEV_1$ in normal subjects or in asthmatics.

These results indicate that cough sensitivity does not directly correlate to bronchial responsiveness in normal and asthmatic subjects.

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Cough is a major respiratory manifestation. Cough and reflex bronchoconstriction often occur simultaneously and have been considered closely related. Contraction of airway smooth muscle was believed by SALEM and AVIADO [1] to be an essential step in the initiation of cough. This hypothesis has been supported by a study of BICKERMAN *et al.* [2] and some subsequent reports [3–8]. Indeed, in some patients with asthma, which bronchial hyperresponsiveness characterizes [9], cough can be a sole manifestation and the cough is relieved by bronchodilators [5, 10]. TAYLOR *et al.* [11] demonstrated that cough threshold to inhaled citric acid correlates to bronchial responsiveness to histamine in cigarette smokers.

However, accumulating data indicate that cough and bronchoconstriction are separate airway reflexes. They can be induced individually [3, 4, 12–14] and can be differentially inhibited by drugs [15, 16]. GIBSON *et al.* [17] reported that cough was not relieved by bronchodilators but improved by steroids in patients with sputum eosinophilia and no bronchial hyperresponsiveness. Moreover, the sensitivity to tussive agents lacks clear relationship both to airway tone and to airway responsiveness to bronchoconstrictor stimuli.

BICKERMAN and BARACH [18] reported that there was no difference in citric acid-induced cough between asthmatics and healthy subjects. The same results were shown by other researchers [19, 20]. Recently, we also found that healthy subjects were as responsive as asthmatics regarding cough sensitivity to inhaled tartaric acid [21].

As mentioned above, airway cough receptor sensitivity seems to be independent from bronchial hyperresponsiveness. However, this hypothesis results indirectly from above mentioned investigations in which the two airway sensitivities were compared between normal subjects and asthmatics or smokers. Asthmatics and smokers have inflammation and increased permeability of airways which may influence both cough receptor sensitivity and bronchial responsiveness. To our knowledge, the direct relationship between airway cough receptor sensitivity and nonspecific bronchial responsiveness has not been reported.

We examined the direct relationship in normal nonsmokers who have no acquired factors modifying cough sensitivity and bronchial responsiveness. Furthermore, we also studied the relationship in asthmatics who have chronic airway inflammation which may heighten the sensitivities.

Materials and methods

Subjects

Thirty eight normal subjects (11 men and 27 women), with a mean age of 21 (range 20–28) yrs, participated in this study. All subjects were

nonsmokers, had no respiratory symptoms and had not experienced a viral infection for at least four weeks. Percent predicted value of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were 103±2% and 105±2%, respectively.

Eleven asthmatic patients (4 men and 7 women), with a mean age of 48 (range 27–67) yrs, were also studied. All patients were nonsmokers and had not experienced a viral infection for at least four weeks prior to the study. Percent predicted value of FVC and FEV_1 were 112±4% and 82±3%, respectively. Each patient satisfied the American Thoracic Society (ATS) definition of asthma, with symptoms of episodic wheezing, cough, and shortness of breath responding to bronchodilators and reversible airflow obstruction documented on at least one previous pulmonary function study [22]. Reversibility was defined as a greater than 15% increase in the FEV_1 following bronchodilator inhalation [23]. The mean value±SD of percentage increase in FEV_1 by inhalation of salbutamol (300μg) was 39±20% (range 16–84%) in the 11 patients. Three men and three women had extrinsic asthma who showed positive allergen skin tests and/or specific IgE antibodies. One man and four women had intrinsic asthma with no familial history of allergic diseases, no increased levels of specific IgE antibodies, and no positive skin test to 10 common allergens. Their symptoms were mild and stable while they were taking oral theophylline, oral or aerosol β_2-adrenergic agonists or mucolytic agents. They had not received steroid therapy for at least 8 weeks. All medication was stopped at 9:00 p.m. on the previous day to allow a washout time of 12 h or more before the tests.

Informed consent was obtained from all subjects. This study was approved by the ethics committee of our university hospital.

Methods

Cough receptor sensitivity to inhaled tartaric acid and nonspecific bronchial responsiveness to methacholine were measured in randomized order at an interval of 2–3 days in each subject.

Measurement of cough sensitivity

Cough sensitivity was evaluated by a tartaric acid inhalation test previously described [24]. Tartaric acid (Wako Pure Chemical Industries, Ltd., Tokyo, Japan) was dissolved in physiological saline to make solutions of 1.56, 3.12, 6.25, 12.5, 25, 50, 100, 200, 400 and 800 $mg \cdot ml^{-1}$. Each subject inhaled a control solution of physiological saline followed by progressively increasing concentrations of the tartaric acid solution. Solutions were inhaled for 15 s by tidal breathing with a nose clip every one minute from a Bennett Twin nebulizer (3012-60cc, Puritan-Bennett Co., Carlsbad, California, USA), and increasing concentrations were inhaled until five or more coughs were elicited. The nebulizer output was $0.21 ml \cdot min^{-1}$. Cough threshold was defined as the lowest concentration of tartaric acid that elicited five or more coughs. To evaluate reproducibility of the cough threshold measurements, the cough threshold was measured twice at 2–3 days interval in nine subjects.

Measurement of bronchial responsiveness

Nonspecific bronchial responsiveness was evaluated by a standardized method recommended by the Japanese society of Allergology using methacholine [25], at the same time of day as measurement of cough threshold, on a separate day within three days. The methacholine challenge test is a two min tidal mouth-breathing method previously described by COCKCROFT *et al.* [26]. 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 and 160 $mg \cdot ml^{-1}$. Saline and methacholine were inhaled from a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, Pennsylvania, USA) operated by compressed air at $5\ l \cdot min^{-1}$. The nebulizer output was $0.14 ml \cdot min^{-1}$. Saline was inhaled first for two minutes and FEV_1 was measured on a dry rolling-seal spirometer (Transfer test, P.K. Morgan Ltd, England). If the change in FEV_1 from the baseline after inhalation of saline was 10% or less in all subjects, inhalation of methacholine was started. Methacholine was inhaled for two minutes by tidal breathing wearing a nose clip, and this was followed immediately by spirometry. Increasing concentrations were plotted on semilogarithmic graph paper and the methacholine provocative concentration producing a 20% fall in FEV_1 ($PC_{20}FEV_1$) was calculated.

Data analysis

Cough threshold and methacholine $PC_{20}FEV_1$ values were expressed as geometric means with the geometric standard error of the mean (GSEM) expressed as a factor. To examine the relationship between cough receptor sensitivity and nonspecific bronchial responsiveness, linear regression and correlation analysis were employed for logarithmic values of the cough threshold and $PC_{20}FEV_1$.

Results

Figure 1 shows the plot for pairs of the tartaric acid cough threshold measurements ($log\ mg \cdot ml^{-1}$) in 9 normal subjects. There was no correlation between the difference and the size of the cough threshold (correlation coefficient (r)=0.035, p=0.9287). The cough thresholds measured at 2–3 days interval were within two doubling concentrations in each subject. As the standard deviation (SD) of differences between the 9 pairs of repeated measurements was $0.251\ log\ mg \cdot ml^{-1}$, the coefficient of repeatability was calculated as $0.502\ log\ mg \cdot ml^{-1}$. So, we considered that there was good reproducibility in the cough threshold measured by the method of this study when the measurements were performed within 3 days.

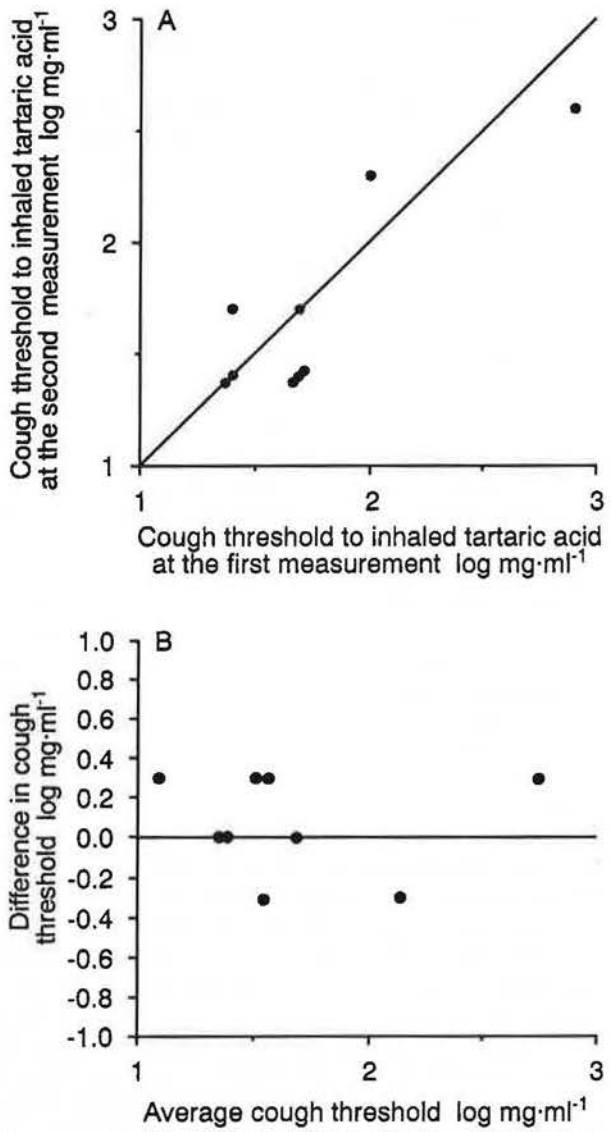

Fig. 1. – Reproducibility of measurement of cough threshold to inhaled tartaric acid in normal subjects. The interval between the first and the second measurement was 2–3 days in each subject. Pairs of log values for the cough threshold measured on 2 separate days are plotted in A, with lone of equality. Averages (X-axis) of and differences (Y-axis) in log values for the cough threshold measured on two separate days are plotted in B.

In 35 out of 38 normal subjects, a cough threshold to tartaric acid was determined at the final concentration or less. No cough was elicited in three subjects at the final concentration of tartaric acid (800 $mg \cdot ml^{-1}$). The cough threshold values for the subjects were assumed to be 1000 $mg \cdot ml^{-1}$ for statistical analysis. The geometric mean value of the cough threshold was 115 $mg \cdot ml^{-1}$ (GSEM1.20). A methacholine PC_{20} FEV_1 value was obtained in 32 subjects. A 20% or greater fall in FEV_1 was not obtained by the final concentration of methacholine (160 $mg \cdot ml^{-1}$) in six subjects. The $PC_{20}FEV_1$ values for them were assumed to be 320 $mg \cdot ml^{-1}$ for statistical analysis. The geometric mean value of the $PC_{20}FEV_1$ was 25.7 $mg \cdot ml^{-1}$ (GSEM1.29). Figure 2 shows the relationship between the cough threshold and bronchial responsiveness in normal subjects. There was no correlation between the cough threshold value to inhaled tartaric acid and $PC_{20}FEV_1$ value to methacholine in normal subjects (correlation coefficient (r)=0.106, p=0.527). When the subjects in whom actual cough threshold or $PC_{20}FEV_1$ value was not determined were excluded, there was also no significant correlation between them.

In all asthmatic patients, the cough threshold and $PC_{20}FEV_1$ were less than the final concentration of tartaric acid (800 $mg \cdot ml^{-1}$) and methacholine (160 mg^{-1}). The geometric mean value of the $PC_{20}FEV_1$ was 0.63 $mg \cdot ml^{-1}$ (GSEM1.29)which was significantly ($p<0.01$) lower than that in normal subjects.

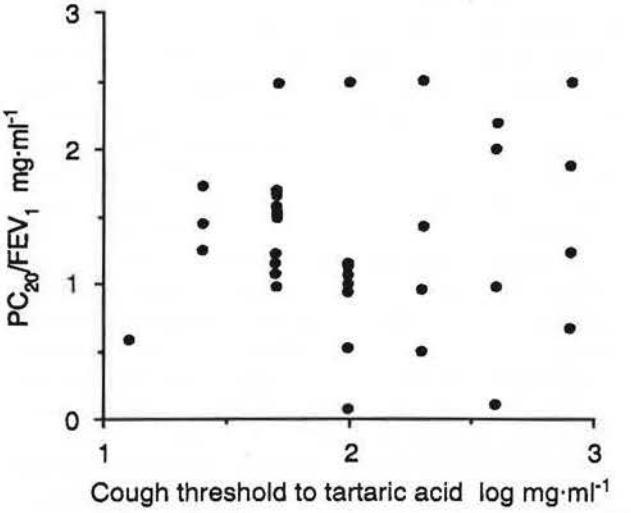

Fig. 2. – Relationship between cough sensitivity to inhaled tartaric acid and nonspecific bronchial responsiveness to methacholine in normal subjects. (n=38) $PC_{20}FEV_1$: provocative concentration of methacholine causing 20% fall in forced expiratory volume in one second.

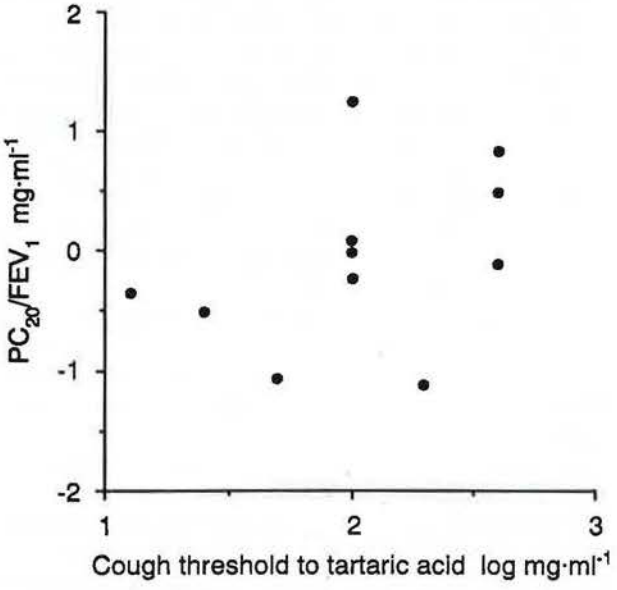

Fig. 3. – Relationship between cough sensitivity to inhaled tartaric acid and nonspecific bronchial responsiveness to methacholine in asthmatic patients. (n=11) $PC_{20}FEV_1$: provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second.

The geometric mean value of the cough threshold was 95.5 mg·ml^{-1} (GSEM1.35) which did not differ significantly from that in normal subjects. Figure 3 shows the relationship between the cough threshold and $PC_{20}FEV_1$ in asthmatic patients. There was no significant correlation between the cough threshold to tartaric acid and $PC_{20}FEV_1$ (correlation coefficient (r)=0.386, p=0.241).

Discussion

In this study, we measured cough threshold to inhaled tartaric acid as an index of sensitivity of airway cough receptors and bronchial responsiveness to methacholine as a parameter of nonspecific bronchial responsiveness in normal and asthmatic nonsmokers. Cough usually results from the stimulation of sensory nerves in the airway. The larynx has two types of cough receptors: myelinated irregularly firing irritant receptors and non-myelinated C-fibre endings. The tracheobronchial tree also has two types of cough receptors: myelinated rapidly adapting stretch receptors (or "irritant receptors") and non-myelinated bronchial C-fibre endings. Cough caused by direct chemical stimulation is considered to result from activation of receptors in the larynx (myelinated or non-myelinated) or activation of bronchial irritant or C-fibre endings, or both [27]. In this study, we used tartaric acid as a cough receptor stimulator. Tartaric acid is a chemostimulant as well as citric acid and may initiate cough by the stimulation of irritant receptors as inhalation of citric acid is associated with a "burning" sensation in the chest [12].

Our study showed no direct correlation of airway cough receptor sensitivity to tartaric acid with nonspecific bronchial responsiveness to methacholine both in normal and asthmatic subjects, and also confirmed that normal subjects are as responsive as asthmatics to inhaled tartaric acid while nonspecific bronchial responsiveness is significantly heightened in asthmatics compared with normal subjects. These findings support the hypothesis that cough and bronchoconstriction are separate airway reflexes.

This hypothesis has been based on the following indirect evidence: 1) cough and bronchoconstriction can be induced separately [3, 4, 12–14]; 2) they can be differentially inhibited by drugs [15, 16]; and 3) there is no difference in induced cough sensitivity between normal and asthmatic subjects while bronchial responsiveness is heightened in the latter [18–21, 28]. Inhalation of nebulized water is a well-known stimulus to both cough and bronchoconstriction in asthmatics [13, 15, 16]. ESCHENBACHER *et al.* [13] found that in asthmatics cough was produced by aerosols with reduced concentrations of permeant anion, whereas an increase in airway resistance occurred when the tonicity of the solution was either below or above isomolarity. It has also been reported that in healthy subjects cough but not bronchoconstriction is induced by solutions with a low concentration of chloride [3, 14]. These findings point to separate mechanisms for the two reflex responses. SHEPPARD *et al.* [15] reported that water-induced cough and bronchoconstriction can be separately inhibited by drugs: the local anaesthetic lidocaine inhibits cough but has no effect on bronchoconstriction, whereas the anti-asthma drug cromoglycate does the opposite. FULLER and COLLIER [16] also reported that cromoglycate does not affect cough caused by distilled water but prevents the bronchoconstriction. It seems generally accepted that bronchial hyperresponsiveness is accompanied by an increased sensitivity to tussive stimili, because a study by EMPEY *et al.* [29] has shown that in subjects with a cold both the bronchial responsiveness to histamine and cough after inhalation of citric acid are stronger than in healthy subjects. According to this view, asthmatics should have a heightened cough sensitivity, but it has been shown that cough induced by citric acid [18–20], capsaicin [28] and tartaric acid [21] is not different between asthmatic and normal subjects. CHOUDRY *et al.* used inhalation of lignocaine to reduce the cough response to inhaled capsaicin, without altering reflex bronchoconstriction in ten volunteers [30]. Taken together, these date indicate that bronchial responsiveness to bronchoconstrictor stimuli is unrelated to the cough sensitivity to inhaled tussive agents.

However, the above hypothesis has been tested indirectly, because in all the above mentioned reports the comparison of cough sensitivity with bronchial responsiveness was made in pathological situations such as upper respiratory tract infection, asthma, cigarette smoking, and so on, which have been shown to modify one of the two sensitivities or both. Accordingly, we studied the direct relationship between cough sensitivity and bronchial responsiveness in normal subjects, both of which are unaffected by any modifiers and widely distributed. In addition, we also examined the relationship in asthmatic patients in order to confirm the previous reports [18–21]. In the results, there was no direct relationship between the two sensitivities both in normal and asthmatic subjects. Consequently, we conclude that airway cough receptor sensitivity is independent from nonspecific bronchial responsiveness. This concept may be important for chest physicians who see patients presenting with cough.

Although it has been established that in some patients with asthma cough can be a sole manifestation, being relieved by bronchodilators [5, 10], we have observed few patients presenting with chronic non-productive cough which is resistant to bronchodilator therapy. Most of them were atopic and responded to histamine H_1-blockers and/or steroids. They had no bronchial hyperresponsiveness and no heightened basal bronchomotor tone [31]. So we speculate that cough may be elicited by two different mechanisms: one is dependent on bronchoconstriction, the other on heightened cough receptor sensitivity but not on bronchoconstriction.

In conclusion, the cough threshold to tartaric acid did not differ between normal and asthmatic subjects, while nonspecific bronchial responsiveness to methacholine was significantly heightened in asthmatics. In addition, there were no correlations between the cough threshold and the bronchial responsiveness in normal and asthmatic subjects. These findings indicate that airway cough sensitivity does not directly correlate to bronchial responsiveness.

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