

Cough Sensitivity in Pure Cough Variant Asthma Elicited Using Continuous Capsaicin Inhalation

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ABSTRACT

Background: Cough variant asthma has recently been described, mainly as airway inflammation in relation to bronchial asthma, but the relationship between the two types of asthma remains unclear. Further studies of cough receptor sensitivity are necessary to fully characterize cough variant asthma.

Methods: We assessed the relevance of testing cough sensitivity using an Astograph[®] with continuous capsaicin inhalation, and compared the results with those obtained using intermittent inhalation. We showed the clinical applicability of testing cough sensitivity (0.156–80 μM capsaicin; five or more coughs, 1 minute of continuous inhalation at each concentration) using this method. We compared cough sensitivity among patients with pure cough variant asthma who did not develop bronchial asthma after an observation period of at least 1 year, patients with bronchial asthma and healthy individuals.

Results: The continuous cough sensitivity test using the Astograph[®] was reproducible and reliable. Cough sensitivity in patients with pure cough variant asthma was significantly higher than that in healthy individuals.

Conclusions: The cough sensitivity of patients with cough variant asthma is not necessarily identical to that of healthy individuals.

KEY WORDS

bronchial asthma, bronchial hyperresponsiveness, cough threshold, wheezing

INTRODUCTION

Cough variant asthma (CVA) is a condition characterized by a chronic dry cough. It has recently been described mostly as airway inflammation in relation to bronchial asthma,^{1,2} but the relationship between the two types of asthma remains obscure. Two cough mechanisms have been considered for CVA: (1) very mild airway constriction unaccompanied by a reduction in pulmonary function or wheezing, and (2) increased cough receptor sensitivity.³⁻⁵ Whereas bronchoconstriction is measured by the airway responsiveness test, the degree of cough receptor sensitivity has not been fully studied to characterize CVA.

Coughing usually results from stimulating sensory nerves in the airway.⁶ Irritant receptors and possibly C-fiber endings are generally recognized as airway

cough receptors.⁷ Capsaicin is the active ingredient of red pepper and it is thought to induce coughing mainly by stimulating C-fiber endings,⁸ although its action may be indirect.⁷ Moreover, O'Connell *et al.*⁹ have investigated the potential role of central cholinergic and dopaminergic receptors in cough mediation by capsaicin, and the potential role of 5-HT receptors in the antitussive action of opiates.

The cough sensitivity test often includes capsaicin. However, the method varies in terms of concentration and the duration of inhalation,¹⁰⁻¹² and has not been standardized. Before investigating patients with cough variant asthma, we assessed the usefulness of the Astograph[®] during continuous capsaicin inhalation without intervals.¹³ We tested cough receptor sensitivity and compared CVA without asthmatic symptoms (pure CVA) with typical bronchial asthma

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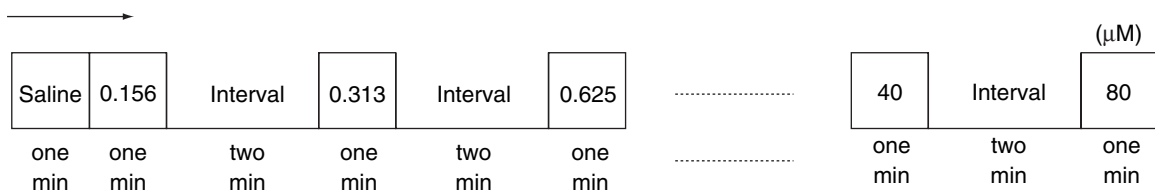
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Intermittent method



Continuous method

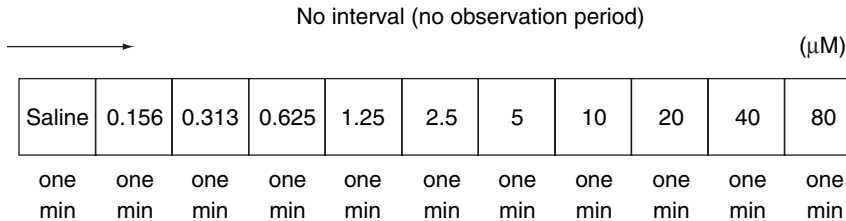


Fig. 1 Cough sensitivity test using intermittent and continuous methods. Two-fold serial dilutions of capsaicin (0.156 – 80 μM) were sequentially inhaled using both methods, from the lowest concentration for 1 minute, until five or 10 coughs were induced.

Table 1 Characteristics of subgroups.

	Typical asthma	Pure CVA	Healthy individuals
Number	22	29	20
Sex (M/F)	7/15	12/17	11/9
Age (y)	49.7 ± 4.1 *	50.9 ± 3.1 *	26.5 ± 0.5
FEV1 (L)	1.82 ± 0.14 *	2.54 ± 0.15 *	3.36 ± 0.16
%FEV1	77.7 ± 4.0 *	96.9 ± 2.6 *	110.2 ± 3.1
C5min (units)	5.8 ± 2.8	5.2 ± 1.9 *	6.4 ± 1.9
Log PD ₃₅ Grs (units)	0.84 ± 0.10	0.81 ± 0.11	

C5min, concentration of inhaled capsaicin required to induce five coughs. PD₃₅Grs, cumulative dose of methacholine when respiratory conductance (Grs) was decreased by 35% from baseline.

**p* < 0.05 vs. healthy individuals.

(typical asthma) .

METHODS

COUGH SENSITIVITY TEST

The Astograph[®] (TCK-6000M, Chest Corp, Tokyo, Japan) assesses bronchial responsiveness to methacholine, and it has been widely applied in Japanese clinical practice.¹³ If the Astograph[®] can be used to evaluate cough sensitivity, it will help to promote testing of this parameter. We examined the usefulness of the method involving the Astograph[®] and continuous capsaicin inhalation without intervals, as described

below. We firstly compared an intermittent method with a 2-minute observation period after inhalation and a continuous method without an observation period to determine the need for observation while increasing the inhaled concentration. The participants comprised 20 healthy non-smokers (11 men; 9 women; mean age, 26.5 ± 2.0 years) without a medical history of respiratory diseases such as bronchial asthma or pulmonary emphysema. None of the participants had a respiratory infectious disease within 2 months of the study, which proceeded in accordance with the guiding principles for human experimentation summarized in the most recent version of the Helsinki Declaration.

Capsaicin (Sigma Chemical, Poole, U.K.) was dissolved in ethanol at a concentration of 1 × 10⁻² mol/l, and 1 ml was added to 9 ml of physiological saline. Thereafter, 2–3 drops of polyoxyethylenesorbitan monooleate 80 (Tween 80) was added to bring the final concentration of capsaicin to 1 × 10⁻³ mol/l. This solution was further diluted to 80 μM and then serially diluted to 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.313 and 0.156 μM. Cough sensitivity was assessed using the Astograph[®]. Participants inhaled sequential capsaicin dilutions for 1 minute, starting with the lowest concentration, until five or 10 coughs were induced, to establish the cough sensitivity threshold. As an evaluation parameter, the concentration at which the total number of coughs per minute was 10 or more was designated as C10min, and its logarithm was designated as LogC10min. Similar parameters were applied using five or more coughs as the index (C5min and LogC5min). We then compared the intermittent

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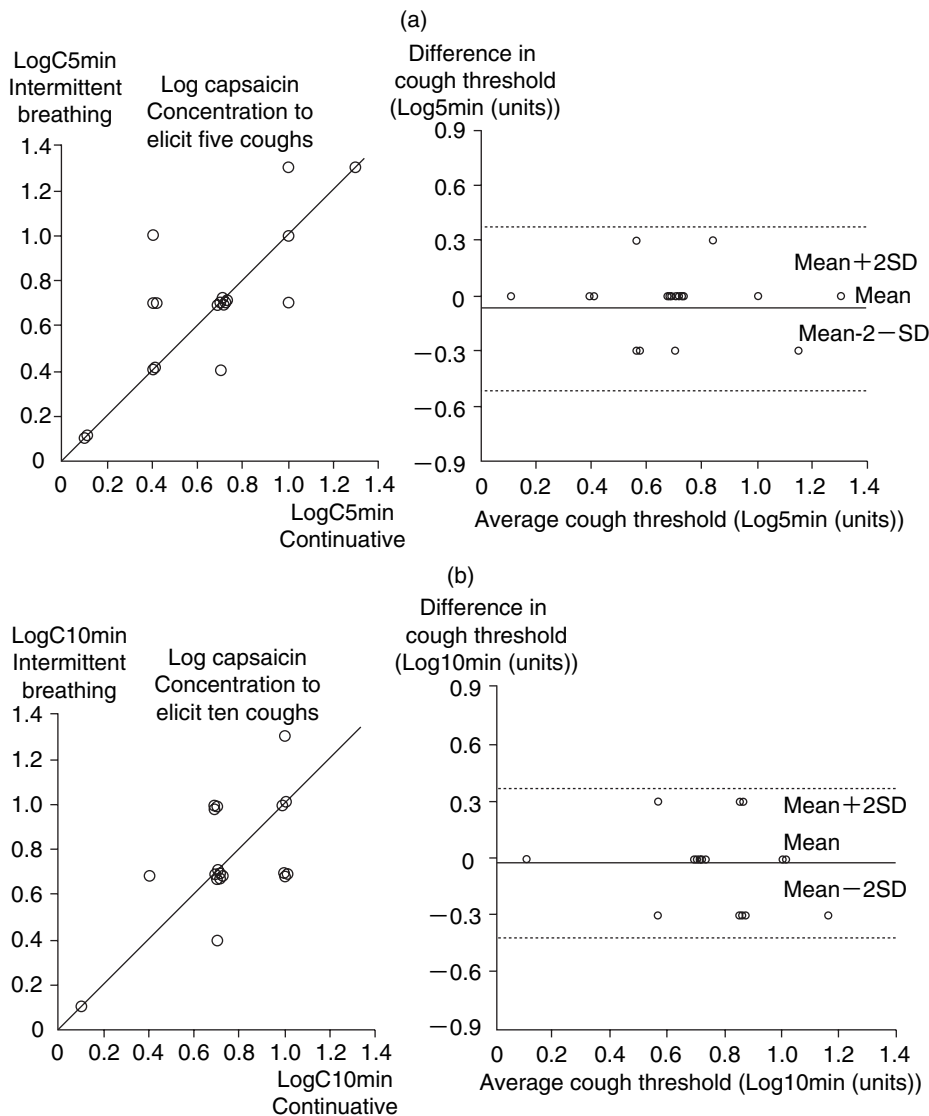


Fig. 2 Effects of intermittent or continuous inhalation on cough threshold to inhaled capsaicin in normal individuals. (a) Log capsaicin concentration required to elicit five coughs (C5min). (b) Log C5min or C10min did not differ between the two methods.

method with a 2-minute observation period after inhaling capsaicin at each concentration and the continuous inhalation method without observation (Fig. 1).

COUGH SENSITIVITY IN PATIENTS WITH CVA

We investigated the cough threshold in 29 non-smoking patients (12 men; 17 women; mean age, 50.9 ± 3.1 years) with CVA using the continuous capsaicin-inhalation cough sensitivity test (Table 1) at the Department of Respiratory Medicine of Kobe University Hospital. Patients with typical asthma for over 1 year were excluded. Patients with subjective paroxysmal dyspnea and wheezing during the first examination, wheezing detected by auscultation, underlying respi-

ratory disease, chronic bronchitis, respiratory infectious diseases within 8 weeks of the first examination and those medicated with ACE inhibitors were also excluded. Twenty-two patients (7 men; 15 women; mean age, 49.7 ± 4.1 years) with bronchial asthma had symptoms typical of wheezing and dyspnea (Table 1). In addition to measurements of cough sensitivity, the patients underwent a detailed inquiry as well as evaluations of pulmonary function and airway hypersensitivity to inhaled methacholine. Each participant provided written informed consent to all procedures associated with the study.

The diagnosis of CVA at the first examination was based on the following findings based on the report of Corrao *et al.*⁶: typical episodes of wheezing and

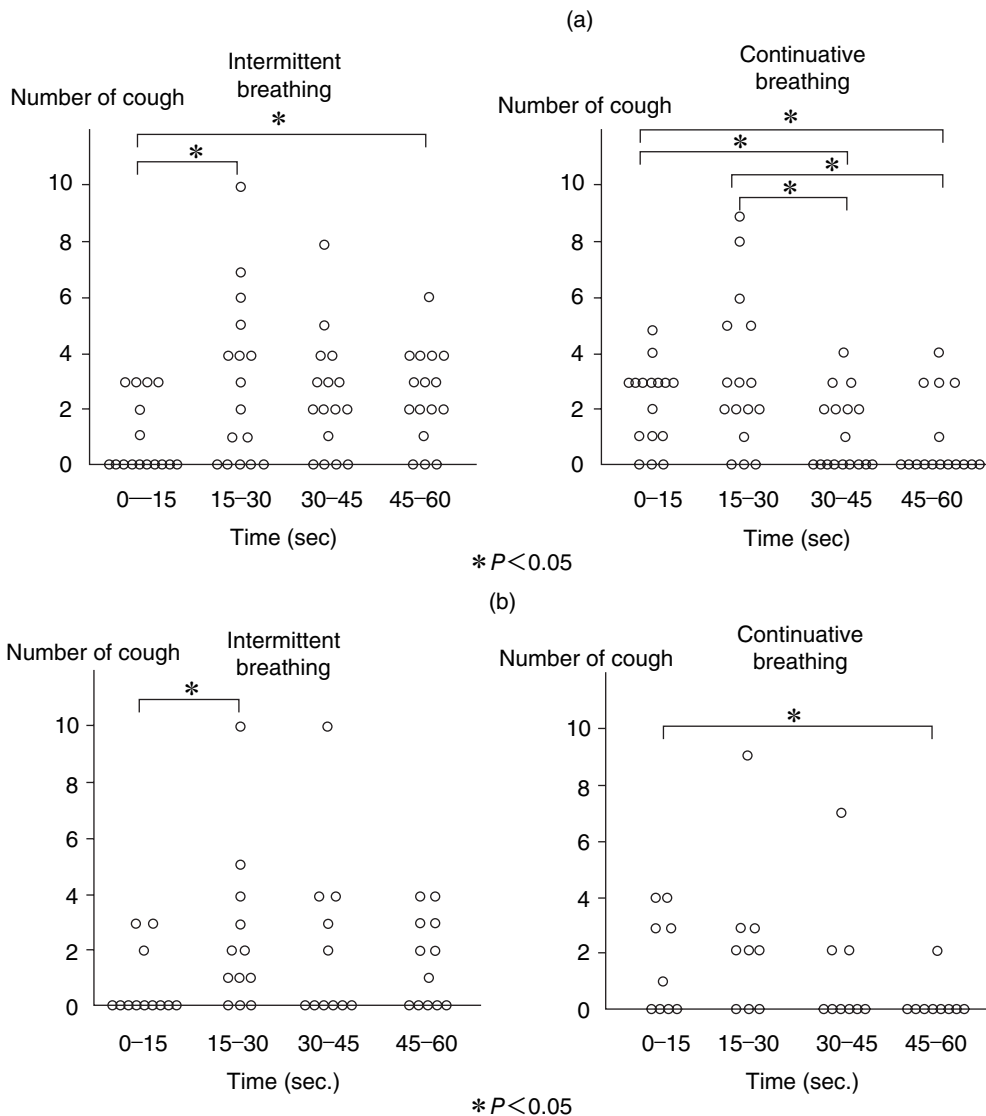


Fig. 3 Number of coughs induced during four consecutive 15-second periods of capsaicin inhalation for 1 minute. (a) Capsaicin inhalation to induce 10 coughs. (b) Capsaicin inhalation required to induce five coughs. Two assessments found no significant differences among any 15-second periods (* $p < 0.05$).

wheezing in auscultation were absent, airway hyper-responsiveness was confirmed by methacholine inhalation, coughing was reduced or resolved by bronchodilators such as oral theophylline or clenbuterol and inhaled β_2 -agonists and CVA did not develop into classical asthma accompanied by wheezing and dyspnea during the observation period.

Cough sensitivity was measured using the Astograph[®]. Two-fold serial dilutions of capsaicin (0.156–80 μ M) were sequentially inhaled for 1 minute without intervals. The concentration required to induce five coughs and its logarithm were designated as C5min and LogC5min, respectively.

PULMONARY FUNCTION TEST

Forced expiratory volume in 1 second, and the ratio (%) of the forced expiratory volume in 1 second were measured using a spirometer (Autospirometer System-55; Minato Medical Science Co., Ltd., Osaka, Japan) during the first examination.

MEASUREMENT OF AIRWAY RESPONSIVENESS

The methacholine inhalation test proceeded as described by Takishima *et al.*¹³ using the Astograph[®]. This instrument can generate dose-response curves of respiratory resistance with tidal breathing during continuous methacholine (two-fold incremental concentrations from 0.049 to 25 mg/ml/min) inhalation.

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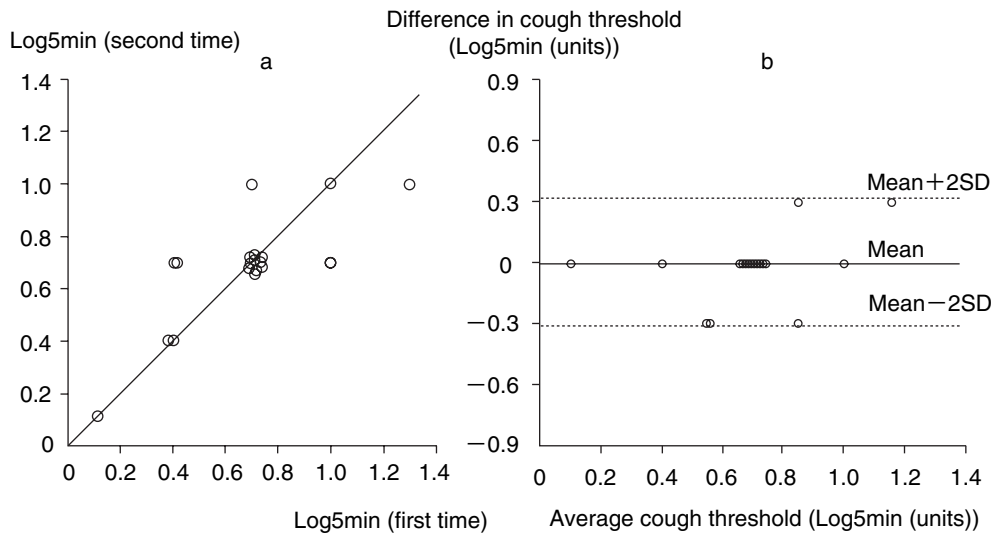


Fig. 4 Reproducibility of induction of at least five coughs by 80 μ M capsaicin. Thresholds determined in the first and second tests did not significantly differ (correlation coefficient, $R = 0.78$).

The following index addressed the pathogenesis of bronchial hyperresponsiveness: cumulative dose of methacholine when respiratory conductance (Grs) was decreased by 35% from the baseline (PD35Grs). All participants were studied between 1 and 3 p.m. Bronchodilators, xanthine derivatives and steroids were not administered for 24 hours before the examination.

STATISTICAL ANALYSIS

All data are expressed as means \pm standard deviation (SD). The C5min and PD35Grs values were statistically analyzed on logarithmically transformed data using the Mann-Whitney U test. Logistic regression was analyzed using StatView J-5.0 (Hulinks Inc. Tokyo, Japan). A p value of <0.05 was taken to indicate a significant difference.

RESULTS

COUGH SENSITIVITY TEST

Figure 2 shows the cough thresholds required to induce five or more coughs and compares the intermittent and continuous methods. The LogC5min and LogC10min values did not significantly differ between the intermittent and continuous methods ($R = 0.795$ $p < 0.01$ and $R = 0.74$, respectively; (Fig. 2a, b). However, in the test investigating the threshold for 10 coughs, 10 or more coughs could not be induced even at the highest capsaicin concentration (80 μ M) in two of 20 patients.

The 1-minute inhalation was divided into 15-second periods, and the frequency of coughing at the cough threshold concentration was determined for each patient (Fig. 3a,b). The frequency was not significantly biased in either method.

The reproducibility of the test inducing five or

more coughs was investigated. A comparison of the cough thresholds obtained in the first and second tests revealed no significant differences and a good correlation (Fig. 4).

COUGH SENSITIVITY THRESHOLD IN PATIENTS WITH COUGH VARIANT ASTHMA

Methacholine-induced airway hyperresponsiveness in pure CVA and typical asthma did not significantly differ (Fig. 5).

The C5min value was significantly lower in patients with pure CVA than in healthy individuals (5.8 ± 2.8 vs. 6.4 ± 1.9 μ M, respectively, $p < 0.05$), indicating that cough sensitivity was increased in the former compared with the latter. However, the value did not significantly differ between pure CVA and typical asthma (Fig. 6).

DISCUSSION

Capsaicin has been widely applied to clinically assess cough sensitivity. Some investigators¹⁰⁻¹² have used the intermittent method with an observation period of about 45 or 60 seconds after inhaling various amounts of capsaicin. Although a standard cough sensitivity test has been established, the applicability of continuous inhalation without intervals to the determination of cough threshold has not yet been defined as an alternative method. In our continuous method, various concentrations of capsaicin were set in the Astograph[®] using a similar protocol to the methacholine challenge test with the following predicted benefits: simple, rapid protocol with a constant maneuver that is straightforward for the participants.

To determine the appropriate duration of capsaicin inhalation, 60 seconds were divided into four 15-second periods, and the frequency of coughing was

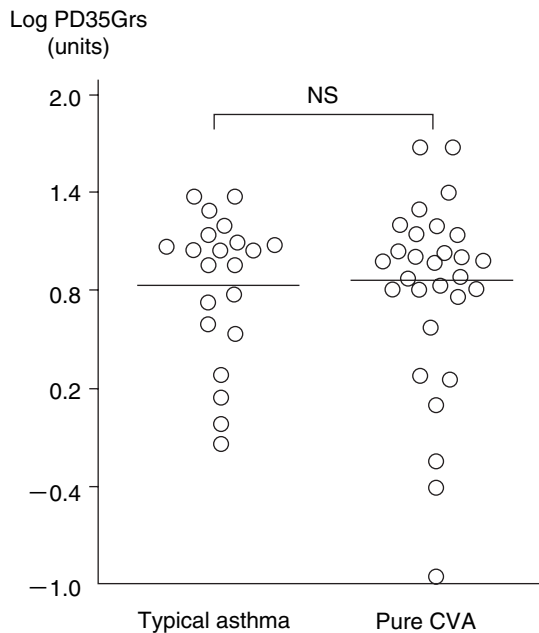


Fig. 5 Bronchial responsiveness to inhaled methacholine in patients with typical asthma and pure CVA. Log PD35GrS did not significantly differ between typical asthma and pure CVA.

determined. Midgren *et al.* reported that when relatively high concentrations of capsaicin (10 and 50 μM) that induce at least 10 coughs are inhaled, most coughs occurred within the first 30 seconds and particularly within the first 15 seconds.¹¹ They described this as being due to partial tachyphylaxis to repeated capsaicin inhalation. Although they also examined concentrations above the threshold, we investigated the cough threshold for over 60 seconds, during which none of the participants developed tachyphylaxis to capsaicin. We propose that inhalation for 60 seconds is necessary because the first 15 seconds is not sufficient to gradually increase the concentration from below the cough threshold for each individual. In addition, the cough threshold was not significantly different between the intermittent and continuous methods, suggesting that an interval is not necessary for executing the cough sensitivity test.

We compared cough thresholds between patients with CVA and healthy controls using continuous capsaicin inhalation. As Corrao *et al.* reported,¹⁴ CVA might be a mild form or a prodrome of bronchial asthma. Although CVA was detected during the first examination, it often clinically developed into bronchial asthma over time. We found that 35% of CVA patients eventually develop asthmatic symptoms of wheezing and dyspnea.¹⁵ Others¹⁶ have suggested that to obtain accurate test findings of pure CVA, a specific observation period might be required and patients who transit to typical bronchial asthma should be excluded. The patients diagnosed with CVA at the

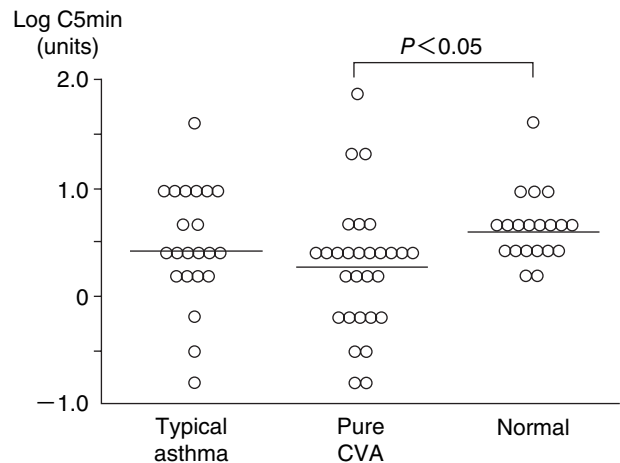


Fig. 6 Cough threshold for capsaicin in patients with typical asthma, pure CVA and normal individuals. Cough threshold (C5min) of patients with pure CVA was significantly lower than that of normal individuals (5.8 ± 2.8 vs. 6.4 ± 1.9 μM ; $p < 0.05$). Log C5min between patients with pure CVA and with typical asthma did not significantly differ.

beginning of the study were actually at a very early stage of bronchial asthma, and thus it is unlikely that these patients actually have pure CVA.

Fujimura *et al.*¹⁷ recently defined atopic coughing as a chronic dry cough, a predisposition to atopy, a negative bronchodilator effect and eosinophilic inflammation in relatively central airways. Their study found that cough receptor sensitivity was increased in atopic cough, but normal in CVA and in bronchial asthma. Although we concur that the mechanisms of airway hyperresponsiveness and cough receptor sensitivity differ, we question whether the levels of cough receptor sensitivity in patients with CVA and bronchial asthma are similar to those of healthy individuals. Cough sensitivity considerably varies when patients with CVA and bronchial asthma are included in one group, but treatment improves coughing as well as cough sensitivity.¹⁶ However, airway hyperresponsiveness and cough sensitivity arise through different mechanisms. Therefore, several causative factors of chronic dry cough, CVA and bronchial asthma in particular, would be present other than atopic cough with increased cough sensitivity.

Thus, we established an observation period of at least 1 year to differentiate relatively pure CVA, excluded patients who transited to bronchial asthma, and defined the remaining patients with CVA as having "pure" CVA. We then compared the cough sensitivity of this group with that of healthy individuals. As noted,¹⁸ the cough threshold between healthy individuals and patients with bronchial asthma did not significantly differ. However, our data showed that the threshold was significantly lower in patients with pure CVA than in healthy individuals. The results of

this study suggested that the cough sensitivity of patients with CVA is not necessarily equal to that of healthy individuals. Some patients who transit to bronchial asthma or who have very early stage bronchial asthma may have been included in the CVA group even after the 1 year observation period. Therefore, a sufficiently long observation period must be established to exclude these patients from the study.

In conclusion, we applied continuous capsaicin inhalation and used an Astograph® to show the clinical usefulness of the cough sensitivity test. In addition, the cough sensitivity of patients with pure CVA that did not develop into bronchial asthma after at least 1 year was significantly higher than that in healthy individuals. Obtaining cough sensitivity information from patients with CVA and with bronchial asthma should help to characterize CVA, and observation for several years might be necessary to accumulate sufficient data.

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