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ORIGINAL ARTICLE

Bronchoconstriction-triggered cough in atopic cough: A retrospective study

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ABSTRACT

Background: Atopic cough (AC) and cough variant asthma (CVA) were identified as major causes of chronic non-productive cough in a Japanese study. A characteristic feature of CVA is the presence of a heightened cough response to bronchoconstriction. On the other hand, the cough response to bronchoconstriction in AC remains unclear. **Methods:** Methacholine (Mch)-induced cough in AC was measured and compared with that in CVA. Diagnoses of AC and CVA were made based on patient history, physical examination, response to bronchodilator therapy, cough reflex sensitivity to capsaicin, spirometry, and airway responsiveness to methacholine. **Results:** Thirteen AC patients and 12 CVA patients in whom the criteria were met were recruited to the study. After inhalation of Mch at PC35-PEF40 that means milder bronchoconstriction than PC20-FEV1, cough was triggered a few times in AC. (cough number: 1/32 min (0–40)). Conversely, significantly greater number of coughs was provoked in CVA, compared with AC (cough number: 35.5/32 min (25–125), $p < 0.05$). **Conclusions:** The cough response to bronchoconstriction is reduced in AC compared to CVA. This feature may be useful in the diagnosis of chronic cough.

ARTICLE HISTORY

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KEYWORDS

atopic cough; cough variant asthma; methacholine

Background

Cough is a common symptom in many conditions and can have a profound impact on health-related quality of life. In a recent large-scale cohort study, the prevalence of prolonged or chronic cough reported as 3.7%.^[1] Both atopic cough (AC) and cough variant asthma (CVA) were identified as major causes of chronic non-productive cough in a Japanese cohort study.^[2] CVA but not AC can also be a precursor of typical asthma.^[3] Therefore, it is important to distinguish between AC and CVA for better long term-management. Isolated measurements of capsaicin provocation test are considered to have no significance due to large variations in cough reflex sensitivity.^[4] The need for a cough reflex provocation test to better discriminate between subjects with cough^[5] and for tailored therapies based on accurate diagnosis has also been identified. We previously identified a heightened cough response to bronchoconstriction as a feature of CVA.^[6] However, the cough response to bronchoconstriction in AC remains unclear. Therefore, this study aimed to investigate the differences between AC and CVA by

retrospectively comparing methacholine (Mch)-induced cough in both conditions.

Methods

Subjects

All subjects gave their informed consent to participate in the study. The diagnosis of either AC or CVA was made according to the following criteria. Thirteen AC patients and 12 CVA patients in whom the diagnostic criteria were completely met were recruited to the study. Characteristics of study participants are shown in Table 1. There were no significant differences in age, height, body weight, and pulmonary function data between the two groups. However, differences were noted in gender, C5, %FVC, FEV1/FVC ratio, PC35-PEF40, and PC20-FEV1.

Study design

Medical records of 115 patients with chronic cough, who visited our clinic between 1st April 2007 and

Table 1. Characteristics of subjects.

	AC	CVA
Number:	12	13
Gender (male/female):	4/9	10/3*
Age (years):	51.6 (18.5)	48.3 (15.6)
Height (cm):	157.2 (9.4)	169.4 (7.6)
Body weight (kg):	55.5 (6.5)	48.3 (15.6)
Complications of allergic diseases:	AD 1, AR 6, UR 1	AR 3, UR 1
Allergens:	CP 5, HDM 2, HDM+CP 1, UK 5	HDM 4, HDM+CP 4, UK 4
C5 ($\mu\text{mol/l}$):	0.56 (0.2)	9.43 (7.7)*
ENO (ppb):	25.5 (16.8)	39.5 (32.4)
Pulmonary function		
FVC (% pred.):	106.5 (18.8)	119.7 (22.4)
FEV ₁ (% pred.):	108.6 (17.7)	109.2 (20.1)
FEV ₁ /FVC ratio (%):	83.7 (8.4)	81.1 (3.7)
Bronchial responsiveness to Mch		
PC35-PEF40 (mg/ml):	4.78 (1.40)	0.80 (1.18)*
PC20-FEV1 (mg/ml):	53.3 (1.40)	4.80 (1.15)*

AC: Atopic cough; CVA: Cough variant asthma; C5: Capsaicin concentration eliciting 5 or more coughs; PC35-PEF40: provocative Mch concentration producing a 35% fall or more in PEF40 from the post-saline value; PC20-FEV1: provocative Mch concentration producing a 20% fall or more in FEV1 from the post-saline value.

Data excluding PC35-PEF40 and PC20-FEV1 were presented as mean $\pm$ standard deviation. PC35-PEF40 and PC20-FEV1 were expressed as geometric mean value with geometric standard error of the mean. * $p < 0.05$ compared with AC group.

AD: atopic dermatitis; AR: allergic rhinitis; UR: urticaria.

CP: cedar pollen; HDM: house dust mite; UK: unknown.

31st March 2013, were retrospectively reviewed. AC and CVA patients who completely met the diagnostic criteria were recruited to the study. Mch-induced cough in AC was measured and compared with that in CVA.

This study was approved by the Medical Ethics Committee of the Kanazawa University Hospital (registration number 1844-1).

Diagnostic criteria for atopic cough

1. Nonproductive cough lasting more than eight weeks without wheezing or dyspnea.
2. Presence of one or more findings indicative of atopy, including a past history and/or complications of allergic diseases excluding asthma, a peripheral blood eosinophilia ($>6\%$ or >400 cells/mL), raised total serum IgE levels (>200 IU/mL), positive specific IgE antibody to aeroallergens, and/or induced sputum eosinophilia ($>2.5\%$).
3. No bronchial reversibility, defined as less than a 10% increase in FEV1 after inhalation of bronchodilator.

4. Bronchial responsiveness within normal limits (provocative concentration of Mch causing a 20% fall in FEV1 (PC20-FEV1) >10 mg/mL).
5. Increased cough receptor sensitivity (capsaicin concentration eliciting five or more coughs (C5) < 3.9 mL).
6. Cough resistant to bronchodilator therapy (oral clenbuterol 40 mg/day plus inhaled procaterol or salbutamol at bedtime and as required for >1 week).
7. No abnormal findings indicative of cough etiology on chest radiograph.
8. Normal FEV1 ($>80\%$ of predicted value), FVC ($>80\%$ of predicted value), and FEV1/FVC ratio ($>70\%$).

Diagnostic criteria for cough variant asthma

1. Isolated chronic non-productive cough lasting more than eight weeks.
2. Absence of a history of wheezing or dyspnea, and no adventitious lung sounds on physical examination.
3. Absence of post-nasal drip to account for the cough.
4. FEV1, FVC, and FEV1/FVC ratio within normal limits (FEV1 $\geq 80\%$ of predicted value, FVC $\geq 80\%$ of predicted value, and FEV1/FVC ratio $\geq 70\%$).
5. Presence of bronchial hyperresponsiveness (PC20-FEV1) < 10 mg/mL).
6. Cough reflex sensitivity within normal limits (C5 ≥ 3.9 $\mu\text{mol/L}$).
7. Relief of cough with bronchodilator therapy.
8. No abnormal findings indicative of cough etiology on chest roentgenogram.

Methacholine inhalation challenge

Increasing concentrations of Mch (0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20, 40, 80, and 160 mg/mL) were inhaled for two minutes by tidal mouth breathing and with the subject wearing a nose clip. This was immediately followed by measurements of partial and full flow-volume curves until the occurrence of a fall of 20% or more in FEV1 (PC20-FEV1) from the post-saline value.^[7]

Partial and full flow-volume curves

Partial and full flow-volume curves were measured as previously described.^[6–8] Partial curves were performed from end-tidal inspiration; upon reaching the residual volume level, subjects inspired to total lung capacity level (deep inspiration) and performed the full curve. The expiratory flow at 40% above residual volume level from the full forced vital capacity was obtained and the volume level was used as the reference volume level to determine the isovolume flow from the partial curve (PEF40).

Methacholine-induced cough

The number of Mch-induced coughs was manually counted by an observer for two minutes during the inhalation and for 30 min after inhalation of Mch at PC35-PEF40 and PC20-FEV1, as previously described.^[6–8] The number of coughs was measured at the two steps of bronchoconstriction. The first step involved a 35% fall in PEF40 from the post-saline inhalation value (PC35-PEF40). PEF40 was used to determine the onset of mild bronchoconstriction to avoid the bronchodilator effects of deep inspiration.^[9] The second step was a 20% fall in FEV1 from the post-saline inhalation value (PC20-FEV1). The decrease in FEV1 at PC35-PEF40 was less than that at PC20-FEV1.^[6–8] Therefore, PC35-PEF40 indicates milder bronchoconstriction than PC20-FEV1.

Data analysis

All data excluded the number of coughs, PC35-PEF40 and PC20-FEV1 was presented as mean $\pm$ standard deviation. Number of coughs was expressed as a median value with range. PC35-PEF40 and PC20-FEV1 were expressed as geometric mean values with geometric standard error of the mean (GSEM). Statistical differences between groups were analyzed using a Mann–Whitney *U* test. PC35-PEF40 and PC20-FEV1 were analyzed using logarithmically transformed values. Values of $p < 0.05$ were considered statistically significant.

Results

Following inhalation of Mch at the PC35-PEF40, few coughs were provoked in AC patients [cough number:

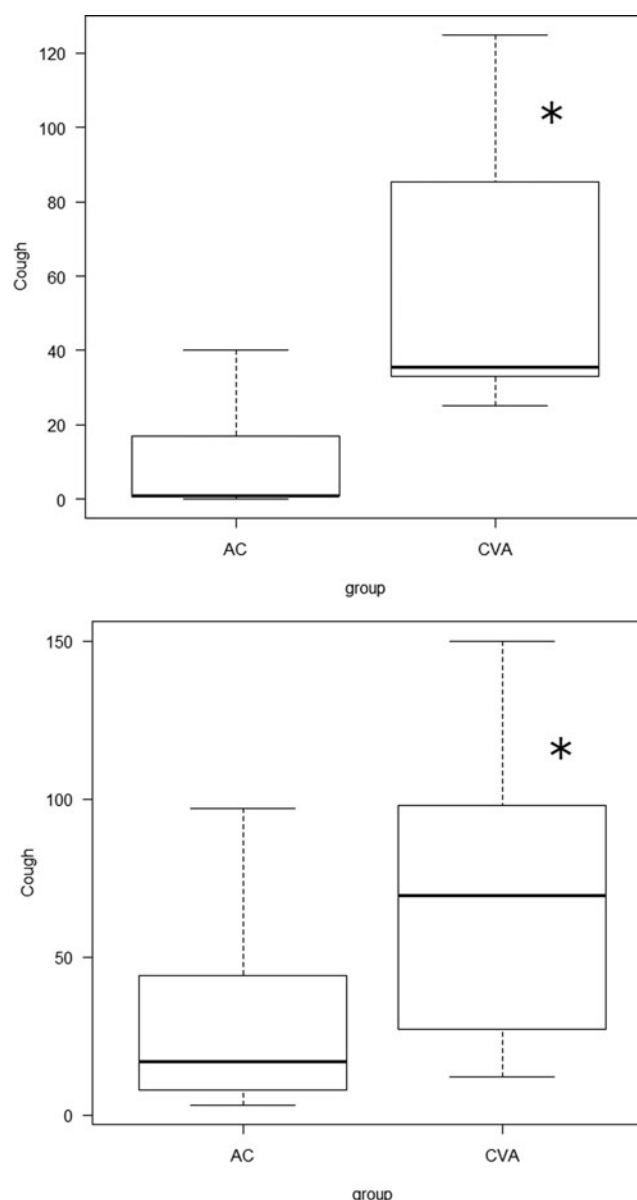


Figure 1. Methacholine-induced cough in patients with atopic cough compared with patients with cough variant asthma. (a, top): After inhalation of methacholine (Mch) at PC35-PEF40, few coughs were provoked in atopic cough (AC) patients [cough number: 1/32 min (0–40)]. Conversely, more coughs were provoked in cough variant asthma (CVA) patients [cough number: 35.5/32 min (25–125)]. (b, bottom): After inhalation of Mch at the PC20-FEV1, coughs were provoked even in AC subjects [17/32 min (3–97)]. However, coughs were provoked to a greater extent in patients with CVA [cough number: 69.5/32 min (18–150)]. * $p < 0.05$ compared with AC group.

1/32 min (0–40)]. Conversely, a significantly greater number of coughs were provoked in patients with CVA compared with AC [cough number: 35.5/32 min (25–125), $p < 0.05$] [Figure 1a]. After inhalation of Mch at the PC20-FEV1, which provoked more severe bronchoconstriction than observed at the PC35-PEF40,

coughs were provoked even in AC subjects [cough number: 17/32 min (3-97)]. Furthermore, coughs were provoked to a significantly greater extent in patients with CVA than in patients with AC [cough number: 69.5/32 min (12-150), $p < 0.05$] [Figure 1b].

Discussion

The data showed that following the induction of mild bronchoconstriction, the number of coughs occurring in AC is lower than that in CVA. The number of coughs observed in AC patients was similar to that seen in normal controls in a previous study.^[6] These results suggest that cough response to bronchoconstriction in AC is similar to normal, despite their heightened cough reflex sensitivity to capsaicin. In contrast, CVA patients have heightened cough response to bronchoconstriction, but their cough reflex sensitivity to capsaicin is not heightened.^[6] Cough sensitivity to capsaicin does not directly correlate to bronchial responsiveness to Mch in normal and asthmatic subjects.^[10-11] In addition, other studies have shown that Mch, which induces bronchoconstriction, may not be an efficacious cough inducer and also that the inhibition of bronchoconstriction does not result in the inhibition of cough.^[11-13] Cough reflex sensitivity to capsaicin was noted to remain unchanged following abrogation of cough after treatment in CVA patients. Conversely, a change in cough reflex sensitivity was noted in AC patients.^[14] There are two possible mechanisms behind non-productive cough: a cough caused by cough reflex hypersensitivity or a cough triggered by bronchoconstriction. We have reported on bronchoconstriction-triggered cough in conscious guinea pigs.^[15] We have also previously shown that the beta2-agonist bronchodilator procaterol completely abolished both Mch-induced bronchoconstriction as well as coughs. These results suggest that coughs induced by Mch are mediated by bronchoconstriction, and that Mch itself does not directly induce cough via chemo-sensors, including C-fibers. We have also shown that capsaicin desensitization has no effect on either Mch-induced bronchoconstriction or coughs. Moguisteine has previously been shown to decrease the excitatory response of rapidly adapting irritant receptors (RARs) to tus-sive stimuli in guinea pigs.^[16] We have also shown that moguisteine dose-dependently inhibits cough, but not Mch-induced bronchoconstriction.^[15] These findings suggest that bronchoconstriction causes cough via

RARs, and not C-fibers. Neither RARs nor C-fibers are involved in Mch-induced bronchoconstriction itself. Canning et al.^[17] have also shown that C-fibers (tracheal/ bronchial irritant receptors also known as cough receptors) are not activated by stimuli that initiate bronchospasms. It is known that although Mch is a bronchoconstrictor, it is not as efficacious a cough inducer as capsaicin or citric acid.^[18] We spent a total of 32 minutes, including a two-minute inhalation time, measuring the number of coughs in each subject. The time taken to measure the number of Mch-induced coughs was longer than for other cough inducers such as capsaicin,^[19] because Mch is a less efficacious direct inducer of cough. We identified the difference between AC and CVA by counting the number of Mch-induced coughs. There is also a possibility that mucus secretion induced by Mch could result in cough as a form of mechanical stimuli, but subjects who take the Mch challenge test do not usually present with a productive cough. Therefore, the data suggests that cough evoked by capsaicin and Mch relies on different afferent pathways. Mch-induced cough appears to be bronchoconstriction-triggered via RARs, not C-fibers. The combination of capsaicin and Mch provocation tests for cough counts may help in the diagnosis of chronic cough. Future work could potentially focus on the development of an efficient method for the evaluation of bronchoconstriction-triggered cough. In terms of treatment strategies and long-term management for chronic cough, it is important to be able to clinically distinguish between CVA and AC because CVA is regarded as a precursor of typical asthma or a pre-asthmatic state, while AC is not. Nearly 30% of CVA patients can develop typical asthma.^[3,20] The main clinical feature of AC is a chronic nonproductive cough resistant to bronchodilator therapy. These patients usually have no history of wheezing or dyspnea, no wheezes audible on auscultation, bronchial responsiveness within normal limits (PC20-FEV1 > 10 mg/mL), a heightened cough reflex sensitivity to capsaicin, and the presence of one or more findings indicative of atopy. This study clearly shows that a new feature of AC is a normal cough response to bronchoconstriction in contrast to CVA.

This study is limited by its use of a small-sized, retrospective cohort, as well as an identified gender bias among the recruited study subjects. Future prospective studies using sex-matched subjects are therefore needed. Furthermore, future studies also need

to take into account the effect of augmented breaths or sighs on bronchospasm or recovery of lung function following Mch challenge. This is because of bronchodilatory response to deep inspiration which affects bronchoconstriction-triggered cough.^[21]

In conclusion, we have identified a novel feature of AC as normal cough response to bronchoconstriction, in contrast to CVA.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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