岩手医科大学
審査学位論文
（博　士）

Original Article

A Comparison of Peripheral Airway Obstruction and Airway Hyperresponsiveness in Patients with Early Bronchial Asthma and Cough Variant Asthma

Takayuki MIYAMOTO, Hiromi NAGASHIMA, Hitoshi KOBAYASHI,
Atsuko SATO, Yu UTSUMI, Yutaka NAKAMURA
and Kohei YAMAUCHI

ABSTRACT

Objectives: Peripheral airway function of cough variant asthma (CVA) and early asthma (EA) has not been fully evaluated. To elucidate this, we used spirometry and the Impulse Oscillometry System (IOS) in patients with EA and CVA and compared peripheral airway function.

Methods: Patients with chronic cough, wheezing and dyspnea within the past 6 months were recruited, and a total of 22 patients with CVA and 42 with EA were studied. After receiving informed consent, we measured FVC, FEV_1, FEF_{75} and FEF50 by spirometry and measured R5 and R20 and X5 using the IOS. Airway hyperresponsiveness (AHR) was measured using a continuous methacholine inhalation method (Astograph; Chest; Tokyo, Japan).

Results: The $FEF_{50}\%$ of patients with EA and CVA were significantly lower than those of controls. Furthermore, both $FEF_{50}\%$ and $FEF_{75}\%$ of patients with EA were significantly lower than those of patients with CVA. The (R5-R20) of patients with EA was significantly higher than that of controls, but there was no difference in (R5-R20) between patients with CVA and controls. D min of patients with EA was significantly decreased compared with that of patients with CVA.

Conclusion: Peripheral airway obstruction and AHR were increased in patients with EA compared with CVA patients. These results suggested that CVA might develop into bronchial asthma with progression of peripheral airway obstruction.

Key words: peripheral airway obstruction, asthma, cough variant asthma, Impulse Oscillometry System, airway hyperresponsiveness

INTRODUCTION

Detection of the early stage of asthma has been

Division of Pulmonary Medicine, Allergy and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine
(Received December 25, 2012)

thought to be important because treatment with inhaled corticosteroid (ICS) is more effective for early asthma (EA) versus chronic asthma.

Cough-variant asthma (CVA) is thought to be a variant form of asthma that usually presents solely with cough alone and no other symptoms such as dyspnea or wheezing.[1] CVA is thought to be a pre-asthmatic

disease since CVA shares several pathophysiological features with bronchial asthma, including eosinophilic airway inflammation, increased airway hyperresponsiveness (AHR), and airway remodeling.[2-7] In a patient with CVA, the first episode of wheezing is thought to be the onset of the asthmatic status. To date, several investigators have reported how some patients with CVA later progressed to develop into asthma with episodic wheezing.[8-11]

Wheezing is caused by turbulence of airflow concomitant with rapid airway narrowing which is closely associated with AHR.[9, 12] Laprise et al. reported that individuals with asymptomatic AHR progressd to asthma along with increasing AHR.[13]

Peripheral airway obstruction has been recognized not only in patients with severe asthma but also in those with mild asthma.[14] With respect to inflammation, eosinophilic infiltration in small airways is stronger than that in the large airways.[15] In addition, peripheral airway obstruction was closely associated with an increase of AHR in asthmatic patients.[16] However, there have been few reports to evaluate both peripheral airway function and AHR of EA.

In this regard, it is important to compare peripheral airway function and AHR between CVA and EA.

The Impulse Oscillometry System (IOS) is a technique used to measure respiratory resistance (R) and reactance (X) at each frequency, and is thus a useful tool for measurement of peripheral airway obstruction. IOS also provides separate measurements for both large and small airway function.[17]

In the present study, we measured pulmonary function of patients with CVA and that of patients with EA with spirometry and IOS and compared the peripheral airway function between these 2 groups of patients. In addition, we compared AHR in these 2 groups. These measurements may allow us to elucidate the process by which CVA develops into asthma.

METHODS

Subjects

Subjects who complained of chronic cough or wheezing or dyspnea within the previous 6 months were recruited at the outpatient clinic in the Division of Pulmonary Medicine, Allergy and Rheumatology of the Department of Internal Medicine at Iwate Medical University School of Medicine from January 2008 to December 2009. This study was approved by the ethics committee of Iwate Medical University.

Study design

Subjects without any chest X-ray findings were recruited into the current study. Healthy subjects without any complaints and with no history of pulmonary diseases were also recruited. Diagnosis was performed based on past history, present history including chronic cough of more than 2 months and episodic wheezing, family history, hematological analysis, immunological analysis and pulmonary function tests including spirometry and AHR test. Subjects with a smoking history of more than 10 pack/year and those who had a history of respiratory infection within the previous 2 months were excluded.

Diagnosis of bronchial asthma was confirmed according to the National Asthma Education and Prevention Program expert panel report 3.[18] Diagnosis of CVA was made according to the following criteria proposed by the Japanese Cough Research Society: 1) Isolated chronic non-productive cough lasting more than 8 weeks; 2) Absence of a history of wheezing or dyspnea and no adventitious lung sounds on physical examination; 3) Absence of postnasal drip to account for the cough; 4) FEV_1, FVC, and FEV_1/FVC ratios within normal limits; 5) Presence of AHR; 6) Relief of cough with bronchodilator therapy; 7) No abnormal findings indicative of cough etiology on chest radiograph.

We screened 210 patients including 115 asthmatics, 39 patients with CVA, 34 patients with acute bronchitis and 22 patients with eosinophilic bronchitis. Asthmatics who had already used inhaled corticosteroid for therapy and those who had asthmatic symptoms longer than 6 months prior to the beginning of the study were excluded.

Asthmatic patients recruited to the present study had not previously been diagnosed as having asthma. In this study, we defined patients with onset of respiratory symptoms within the previous 6 months as EA.

In the present study, we studied 42 patients with EA

Table 1 Comparison of pulmonary function among early asthmatics, patients with cough variant asthma and normal subjects.

	Control (C)	Early asthma(EA)	Cough variant asthma (CVA)	Statistical analysis		
				EA/C	CVA/C	EA/CVA
Number (men/wemen)	11 (5/6)	42 (17/25)	22 (6/16)	NS	NS	NS
Age (years)	45 (26-56)	35.5 (19-73)	42 (20-83)	NS	NS	NS
Height (cm)	157 (152-183)	157.5 (142-189)	157 (141-177)	NS	NS	NS
Weight (kg)	57 (44-85)	57.5 (42-90)	58 (47-79)	NS	NS	NS
IgE (IU/mL)	—	225.5 (2-1300)	43.5 (2-234)	—	—	$p<0.01$[†]
D min (unit)	—	1.05 (0.09-6.2)	2.45 (0.12-9.49)	—	—	$p<0.05$[†]
%FEV_1 (%predicted)	103 (97.9-123.9)	102.85 (58.9-134)	108.45 (73.7-136.8)	NS	NS	NS
FEV_1% (%)	83.72 (73.42-92.6)	78.2 (53.88-89.86)	82.73 (68.3-87.7)	$p<0.05$[‡]	NS	NS
FEF_{50}% (%predicted)	96.7 (71.2-137.2)	58.6 (13.7-124.8)	82.45 (51.8-102.7)	$p<0.001$[††]	$p<0.05$[††]	$p<0.05$[††]
FEF_{75}% (%predicted)	71.1 (36.1-114.8)	39.7 (11.6-75.5)	51.6 (27.6-76.5)	$p<0.01$[‡]	NS	$p<0.05$[‡]

FEV_1, forced expiratory volume in one second; FEV_1%, the value that divided FEV_1 by forced vital capacity; FEF_{50}, forced expiratory flow 50%; FEF_{75}, forced expiratory flow 75%; D min, the minimum dose of methacholine as a measure of bronchial responsiveness; lgE, immunoglobulin E.
Data are expressed as medians (minimum–maximum). [†]Cochran-cox, [‡]Dunn's test, [††]Scheffe test.

(men : women, 17 : 25; age, 35.5 (19–73) years old), 22 patients with CVA (men : women, 6 : 16; age, 42 (20–83) years old) and 11 healthy subjects (men : women, 5 : 6; age, 45 (26–56) years old). Data are expressed as a median (range).

Pulmonary function

Spirometry was performed at the first visit in all subjects. VC, FVC, FEV_1%, FEV_1, FEF_{50} and FEF_{75} were evaluated by CHESTAC-8800 (Chest, Tokyo, Japan).

AHR to methacholine was measured using the Jupiter 21 Astograph (Chest, Tokyo, Japan) as previously reported.[19] Briefly, AHR was tested by directly recording the dose-response curve of Rrs (cmH$_2$O/L/sec) during the continuous inhalation of methacholine in two-fold incremental concentrations (49 to 25,000 g/ml), under tidal breathing from nebulizers with an output of 0.15 ml/minute. If bronchodilators were being used, their use was suspended for 24 hours prior to methacholine inhalation. In brief, after we recorded the baseline Rrs during the inhalation of physiologic saline for 1 minute, patients inhaled methacholine, starting with the lowest concentration, at 1-minute intervals. The index of airway sensitivity that we adopted was D min defined as the cumulative dose of inhaled methacholine at the inflection point where Rrs began to increase continuously. One D min unit is equivalent to a dose of 1 mg/ml methacholine inhalation for 1 minute.

We also employed the Impulse Oscillometry System (IOS) (Master Screen IOS; Jaeger, Wurzburg, Germany) in a subset of patients with EA (n=13) and CVA (n=14). Data are expressed as medians and range. After IOS, the following parameters were evaluated: 1) airway resistance at 5 Hz (R5), total index influenced by both large and small airways; (2) airway resistance at 20 Hz (R20), an index of large airways; (3) the value obtained by subtracting R5 from R20 (R5-R20), an index of the frequency dependence of resistance, which is reflective of small airway function; (4) reactance at 5 Hz (X5), considered to indicate the capacitive reactance in small airways.[20-22]

Statistics

We performed statistical analysis using Stat Mate (Atoms, Tokyo, Japan) and Stat Light (Yukms, Tokyo, Japan). Comparison of data among the three groups were performed using the one-way ANOVA. In post-hoc analysis, comparison of the data of two groups were performed by the Scheffe test for normal distribution and by the Steel test and Dunn's tests for nonnormal distribution. Differences of D min and serum IgE between patients with EA and those with CVA were analyzed by the Cochran-Cox. p values of less than 0.05 were considered statistically significant.
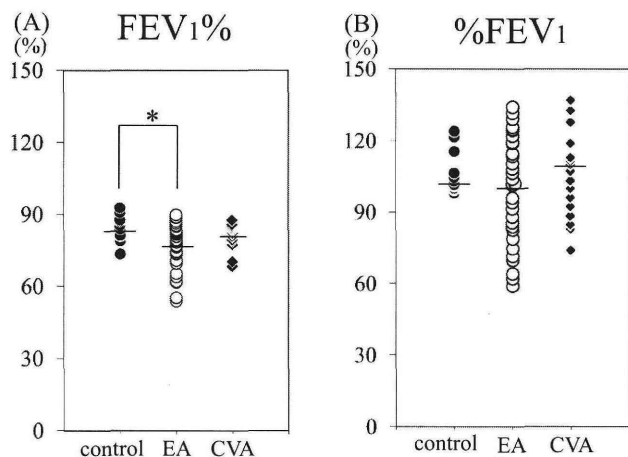
Fig. 1 Panel A: Comparison of $FEV_1\%$ among controls, EA and CVA patients. $^*p < 0.05$, Scheffe test. Panel B; Comparison of % FEV_1 (% predicted) among controls (n = 11), patients with EA (n = 42) and CVA (n = 22). Bars indicate median values.
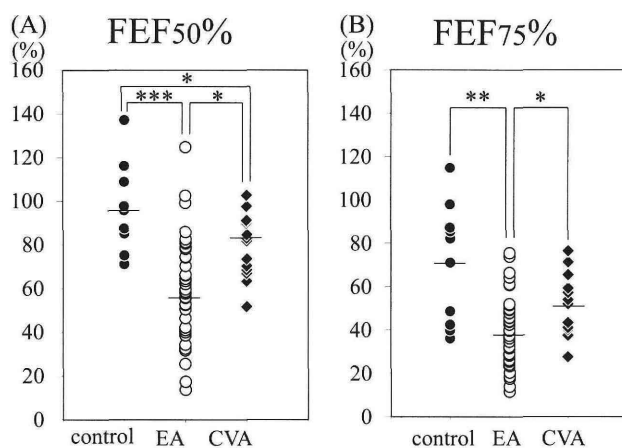

Fig. 2 Panel A: Comparison of $FEF_{50}\%$ among controls, EA and CVA patients. $^{***}p < 0.001$, $^*p < 0.05$, Scheffe test. Panel B: Comparison of $FEF_{75}\%$ among controls, EA and CVA patients. $^{**}p < 0.01$, $^*p < 0.05$, Scheffe test. Bars indicate median values.
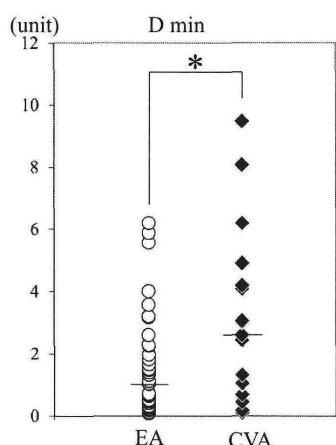

Fig. 3 Comparison of D min between EA and CVA patients. $^*p < 0.05$, Cochran-Cox.
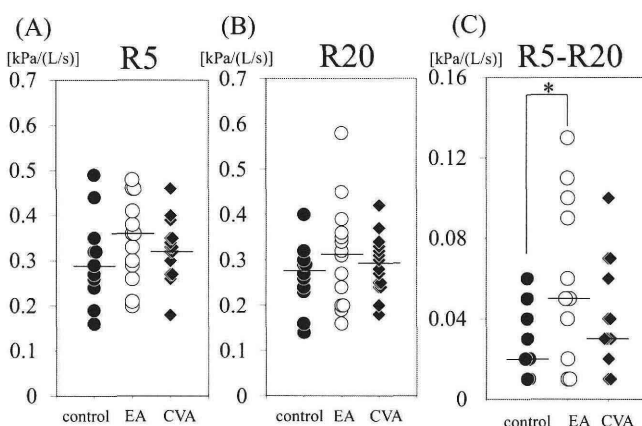

Fig. 4 Panel A: Comparison of R5 in IOS among controls (n = 9), EA (n = 13) and CVA patients (n = 13). Panel B: Comparison of R20 in IOS among controls, EA and CVA patients. Panel C: Comparison of (R5-R20) in IOS among controls, EA and CVA patients. $^*p < 0.05$, Dunn's test. Bars indicate median values.

RESULTS

Spirometric analysis in patients with EA and CVA (Table 1)

There was no significant difference in age, gender ratio, height, and weight among the 3 groups of subjects including controls, patients with EA and CVA. Serum IgE level in patients with EA was significantly higher than those of CVA ($p < 0.01$). Spirometry was performed in 3 groups of subjects including controls, patients with EA and CVA. There was significant difference in $FEV_1\%$ between controls and patients with

EA (Fig. 1A). But there was no significant difference in the $\%FEV_1$ (% predicted) among the 3 groups (Fig. 1B). In contrast, there were significant differences in $FEF_{50}\%$ among the 3 groups (control vs EA: $p < 0.001$, control vs CVA: $p < 0.05$, EA vs CVA: $p < 0.05$) (Fig. 2A). In addition, the $FEF_{75}\%$ values for patients with EA were significantly lower than those of controls and patients with CVA (control vs EA: $p < 0.01$, EA vs CVA: $p < 0.05$) (Fig. 2B).

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Table 2 Comparison of peripheral airway function among early asthmatics, patients with cough variant asthma and normal subjects.

	Control (C)	Early asthma(EA)	Cough variant asthma (CVA)	Statistical analysis		
				EA/C	CVA/C	EA/CVA
Number (men/wemen)	11 (5/6)	13 (5/8)	14 (5/9)	NS	NS	NS
Age (years)	45 (26–56)	45 (21–73)	41 (20–76)	NS	NS	NS
Height (cm)	157 (152–183)	158 (142–181)	157 (153–177)	NS	NS	NS
Weight (kg)	57 (44–85)	58 (44–88)	63 (48–79)	NS	NS	NS
R5 (kPa/(L/s))	0.29 (0.16–0.49)	0.36 (0.21–0.48)	0.33 (0.18–0.46)	NS	NS	NS
R20 (kPa/(L/s))	0.27 (0.14–0.4)	0.32 (0.16–0.58)	0.29 (0.2–0.42)	NS	NS	NS
R5—R20 (kPa/(L/s))	0.02 (0.01–0.06)	0.05 (0.01–0.13)	0.03 (0.01–0.1)	$p < 0.05^{\dagger}$	NS	NS
X at 5 Hz (kPa/(L/s))	−0.12 (−0.16–0.05)	−0.12 (−0.18– −0.09)	−0.11 (−0.18– −0.05)	NS	NS	NS

Data are expressed as medians (minimum−maximum).
R5, resistance of the respiratory system at 5 Hz; R20, resistance of the respiratory system at 20 Hz; R5-R20, difference of R5 and R20; X5, reactance of the respiratory system at 5 Hz. †Steel test.
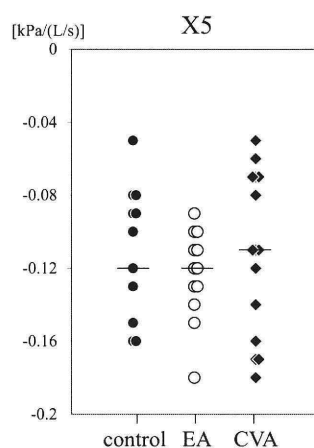

Fig. 5 Comparison of reactance of the respiratory system at 5 Hz (X5). Bars indicate median values.

Comparison of AHR between EA and CVA

AHR of patients with EA and CVA was compared. D min of EA patients was significantly lower than that of the CVA patients (p<0.05) (Fig. 3 and Table 1).

IOS analysis in EA and CVA

There was no significant difference in either R5 or R20 among the 3 groups. However, only (R5-R20) of EA was significantly higher than that of the controls (p<0.05) (Fig. 4 and Table 2). There was no significant difference in X5 among the 3 groups (Fig. 5 and Table 2).

DISCUSSION

The present study demonstrated differences in pulmonary functions among control subjects, patients with CVA and patients with EA. FEV$_1$%, FEF$_{50}$% and FEF$_{75}$% in spirometry were significantly reduced in patients with EA compared with controls. FEF$_{50}$% and FEF$_{75}$% were significantly reduced in patients with EA compared the patients with CVA. D min in EA was significantly lower than that in patients with CVA. In addition, (R5-R20) increased significantly in EA patients compared with controls. These results suggested that airway obstruction especially in the peripheral airway was more developed in patients with EA compared with patients with CVA and controls.

CVA was described by Corrao et al.[1] as a disease in which cough may be the sole presenting symptom. CVA shares a number of pathophysiological features with classic asthma, such as atopy, AHR, and eosinophilic airway inflammation. Fujimura et al. also reported that 8 of 55 patients with CVA (15%) developed wheezing or dyspnea during a median follow-up period of 3.7 years.[10] Recently, Matsumoto et al. reported that 6 of 20 patients with CVA (30%) who did not receive ICS treatment progressed to classic asthma, whereas only 2 of 35 patients (6%) treated with ICS had such progression.[11] These results suggested that CVA is a pre-asthmatic disease that can develop into classic asthma. In addition, progression of CVA into asthma may be modified by ICS treatment.

Wheezing is a cardinal symptom of asthma and is associated with both airway obstruction and turbu-

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lent airflow.[23] Shim et al. reported that there was a relationship between the characteristics of wheezing and the severity of airways obstruction.[24] In this regard, worsening of airway obstruction is thought to be a critical factor in progression of CVA into classic asthma. The present study revealed that both $FEF_{50}\%$ and $FEF_{75}\%$ in EA were significantly lower than those in patients with CVA. These results suggested that peripheral airway obstruction was more advanced in EA than in CVA. Consistent with this premise, using IOS, we found that (R5-R20) in patients with EA was significantly higher than that in control subjects, whereas no significant difference in (R5-R20) between patients with CVA and the control subjects were observed in the present study.

Niimi et al. reported that $FEV_1\%$ (predicted) and $MEF_{25}\%$ (corresponding to $FEF_{75}\%$ in our paper) of both classic asthma and CVA patients were significantly lower than those of control subjects, but there was no significant difference in $MEF_{25}\%$ (% predicted) values between classic asthma and CVA.[3] Here, we were able to detect significant differences in $FEF_{50}\%$ and $FEF_{75}\%$ between EA and CVA. Reasons for this discrepancy between Niimi et al. and our study stil remain unclear. However, we assume that use of treatment including ICS by patients in the study of Niimi et al. might be partially responsible; measurement of the pulmonary function in our study was performed in patients who had not receive treatment.

AHR is thought to be a critical physical characteristic in the pathogenesis of asthma. Laprise et al. reported that some asymptomatic subjects with AHR progress to symptomatic asthma concomitant with an increase in AHR.[13, 25] Fujimura et al. reported that the PC_{20} values in patients with CVA who developed typical asthma were significantly lower than those in patients who did not develop typical asthma.[10] Wheezing, a cardinal symptom of asthma, has been thought to be caused by turbulence of airflow concomitant with rapid airway obstruction, induced by contraction of smooth muscles in the airway.[12] Wheezing is therefore closely associated with increased AHR.

We demonstrated that AHR, expressed as D min, was significantly decreased in patients with EA com-

pared with patients with CVA. Niimi et al. reported there was no difference in AHR between patients in CVA and typical asthma.[3] We believe this discrepancy may be attributed to the fact that asthmatics studied by Niimi et al. had been treated, as described above. In our study, we recruited patients with early stage asthma who complained of symptoms within the past 6 months and had not been treated previously. For this reason, we might have been able to detect a difference in AHR between patients with EA and those with CVA.

We measured the peripheral airway function of patients with EA and CVA by IOS, considered an alternative method to spirometry that is more sensitive at measuring small airway dysfunction and recognizing subtle changes within the airway.[26, 27] Frequency-dependent changes in resistance have been demonstrated in small airway disease.[28] The difference between R5 and R20 (R5-R20), as an index of frequency dependence of resistance, was reported to be a sensitive index of peripheral airway obstruction.[20] However, there was no significance in the (R5-R20) between patients with EA and those with CVA. One probable reason may have been the small number of subjects studied. Larger patient populations may have been required to evaluate these results more accurately.

In our study, we demonstrated a small but significant increase in peripheral airway obstruction in EA compared with CVA. Allergic rhinitis is also an allergic airway disease associated with airway inflammation similar to that in asthma. As with CVA, some patients with allergic rhinitis developed asthma due to progress of AHR.[29, 30] In addition, Marseglia et al. demonstrated peripheral airway obstruction in patients with allergic rhinitis and suggested a link between allergic rhinitis and asthma.[31] Ohrui et al. reported that peripheral airway obstruction was closely associated with AHR.[16] Taking these findings into consideration, our results suggest that some patients with CVA might develop asthma resulting from progress of peripheral airway obstruction.

CONCLUSIONS

Peripheral airway obstruction was significantly in-

creased in both patients with EA and CVA compared with controls. Furthermore, peripheral airway obstruction and AHR were increased in EA patients compared with CVA patients. These results suggested that CVA might develop into bronchial asthma resulting from progress of peripheral airway obstruction.

DECLARATION OF INTEREST

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