
◎原 著

Correlation between decrease in %FVC and airway inflammation in patients with asthma, classified by clinical symptoms

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Summary:Clinical features of asthmatics with a low %FVC (<80%) were studied in relation to airway inflammation and clinical asthma types. 1. Twenty four (75.0%) of the 32 subjects with a low %FVC had steroid-dependent intractable asthma. 2. A significant association between %FVC value and clinical asthma type was found. The value of %FVC was significantly lower in subjects with type II asthma (bronchiolar obstruction), in which significantly decreased proportion of lymphocytes, and significantly increased proportion of neutrophils in bronchoalveolar lavage (BAL) fluid were observed, than in those with type Ia-1 (simple bronchoconstriction) with ($P<0.001$) and without glucocorticoid therapy ($P<0.02$). 3. The %FVC value was significantly improved after treatment in type Ib (hypersecretion) with BAL eosinophilia, but not in those with type II with BAL neutrophilia. These results demonstrate that marked decrease of %FVC in patients with asthma correlated with airway inflammation, and that airway reversibility by medication is very low in patients with type II asthma.

Key words:ventilatory function, FEV1.0, bronchoalveolar lavage, bronchial reversibility

Introduction

When a relevant allergen is inhaled by patients with

asthma, airway narrowing develops at two different phases; within 30 min of the inhalation (immediate asthmatic reaction, IAR), and within 6 to 8 hours (late

asthmatic reaction, LAR)(1-3). The magnitude and duration of hyperresponsiveness are speculated to be related to the LAR (4, 5), which is associated with migration of inflammatory cells, predominantly activated T lymphocytes and eosinophils, into the airways (6, 7). Thus, airway inflammation is a common feature in asthma (8-11), leading to decrease in bronchial reversibility by medications.

We previously reported (12-15) that asthma can be classified by clinical symptoms into three clinical types, which are closely related to airway inflammation; type Ib asthma is characterized by increased proportion of eosinophils (16) in bronchoalveolar lavage (BAL) fluid, and type II asthma by increased proportion of BAL neutrophils. Our studies also showed that ventilatory parameters such as FEV1.0 and V25 are affected by the proportion of inflammatory cells in the airways (12).

Airway narrowing caused by inhalation of allergen and the other stimuli can be estimated by measuring ventilatory function, routinely by a 20% fall in forced expiratory volume in 1 second (FEV1.0), which is the most common in clinical examination. The airway narrowing is often improved immediately after inhalation of bronchodilators. Many of patients with asthma show a predominant decrease in FEV1.0%, however, some of patients have a predominant decrease in forced vital capacity (FVC). In this study, clinical features of asthmatics with a low %FVC were analyzed in relation to clinical asthma type and airway inflammation.

Subjects and Methods

The subjects of this study were 32 asthmatics (12 females and 20 males) with a low %FVC under 80%. Their mean age was 61.0 years (range 23-77 years), and the age at onset was 45.2 years (range 3-73 years). The subjects were divided into 4 groups according to the value of %FVC; 75-79%, 70-74%, 60-69% and \leq 59%, and 4 groups by age; 20-49, 50-59, 60-69, and 70+ years. All subjects were admitted at our hospital

and had drug medication and spa therapy (17, 18) for 1-3 months.

Asthma classification was performed by the method previously described (12, 13); Ia. simple bronchoconstriction type, Ib. bronchoconstriction + hypersecretion type, and II. bronchiolar obstruction type. The criteria were as follows:

Type Ia. Simple bronchoconstriction type: Patients with symptoms such as wheezing and dyspnea which are mainly elicited by bronchoconstriction. In this study, we divided this type into two subtypes according to the amount of expectoration: 0-49 ml/day (Type Ia-1) and 50-59 ml/day (Type Ia-2).

Type Ib. Bronchoconstriction + hypersecretion type: Patients with symptoms due to hypersecretion (more than 100 ml/day of expectoration), in addition to bronchoconstriction.

Type II. Bronchiolar obstruction type: Patients with symptoms mainly elicited by bronchiolar obstruction.

Furthermore, subjects with type Ia-1 were divided into two groups; with (S+) and without long-term regimen of glucocorticoids (S-).

BAL was carried out according to a previously reported method (19-21) when the subjects were attack-free. Informed consent for this BAL procedure was obtained from all study subjects. The aspirates obtained by BAL were filtered through a sterile steel mesh, and the filtrates were centrifuged at 300 g for 10 min at 4 °C, and the cell pellet was resuspended in Tris ACM. Smear preparations were made using the cell suspension. The slides were air dried and stained with May-Giemsa stain. A differential cell count was performed on 500 cells excluding epithelial cells. In this study, the mean recovery rate was $26.8 \pm 9.5\%$ (mean \pm SD). The total number of cells aspirated in the BAL fluid was $9.53 \pm 10.2 \times 10^6$. The results were expressed as a percentage of the total cells.

Ventilatory function tests, using a Box Spirometry 81S (Chest Co) were carried out in all patients when they were asymptomatic.

The level of serum cortisol was measured by

radioimmunoassay (RIA) at 7 to 8 o'clock in the morning within a few days after their admission.

Statistically significant differences of the mean were estimated using the unpaired and paired Student's *t* test. A *p* value of <0.05 was regarded as significant.

Results

Twenty four (75.0%) of the 32 subjects were evaluated as having steroid-dependent intractable asthma (SDIA), since they had been treated with oral glucocorticoids (5-20 mg/day of prednisolone) and inhaled glucocorticoids (200-600 μ g/day of beclomet-hasone) for more than 2 years. All of the 8 patients without SDIA had type Ia-1 asthma.

Table 1 shows characteristics of subjects classified by the value of %FVC. The level of serum cortisol was lowest in subjects with %FVC between 70 and 74%. The difference in serum cortisol levels was not significant among the four groups. Mean age and age at onset were lowest in patients with %FVC between 60 and 69%, however, any correlation was not found between age and %FVC value (Fig.1).

Table 2 shows a correlation between ventilatory function and the proportion of BAL cells in the four clinical asthma types. The %FVC value was significantly lower in patients with type II asthma than in those with type Ia-1 (S-; *p*<0.02, S+; *p*<0.001) (Fig.2). The value of FEV 1.0% was not significantly different among the four asthma types (Fig.3). Regarding the proportion of BAL cells, the proportion of BAL lymphocytes was significantly lower in patients with type II asthma than in those with type Ia-1 (S-) (*p*<0.05). The proportion of BAL neutrophils was significantly larger in patients with type II asthma than in those with type Ia-1 (S-; *p*<0.001, S+; *p*<0.001) and type Ib (*p*<0.05). In contrast, the proportion of BAL eosinophils was significantly larger in patients with type Ib compared to that in those with type Ia-1 (S-; *p*<0.02, S+; *p*<0.005).

To assess whether a low FVC value in these patients is reversible or not, the value was compared before

Table 1. Characteristics of asthma patients with a low %FVC studied

%FVC	No of patients	Age (years)	Age at onset (years)	IgE (IU/ml)	S-Cortisol
75-79 %	11	60.5	41.1	460 (16-1020)	6.8 (2.4-15.9)
70-74 %	10	61.3	46.2	211 (27- 546)	4.8 (1.6-12.1)
60-69%	4	55.0	35.0	759 (237-1962)	6.2 (1.0-13.2)
≤59 %	7	64.7	56.1	873 (106-2798)	8.1 (1.3-16.2)

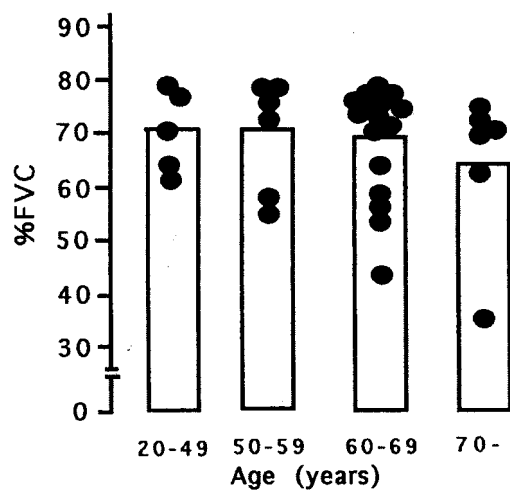


Figure 1. Correlation between %FVC value and age in asthma patients with a low %FVC.

Table 2. Ventilatory function and cellular composition of BAL fluid in patients with asthma classified by clinical symptoms

Asthma type	No of subjects	%FVC	FEV1.0%	Mac	Lym	Neut	Eos
Ia-1(S-)	8	72.3 ^a ± 7.7	60.9 ± 6.6	79.4 ± 9.8	17.2 ^c ± 6.7	1.3 ^d ± 1.3	2.2 ^g ± 1.7
Ia-1(S+)	8	75.2 ^b ± 4.0	64.8 ± 13.0	79.8 ± 12.2	14.7 ± 11.8	1.3 ^e ± 0.8	4.2 ^h ± 4.5
Ia-2	5	67.8 ± 6.3	62.4 ± 7.1	74.3 ± 8.6	12.8 ± 4.3	5.7 ± 6.2	7.0 ± 6.1
Ib	5	70.0 ± 10.1	60.8 ± 3.7	68.7 ± 18.8	14.7 ± 5.5	1.4 ^f ± 1.2	15.2 ^{gh} ± 13.4
II	6	55.1 ^{ab} ± 14.7	47.7 ± 10.4	44.1 ± 22.2	5.3 ^c ± 8.6	39.4 ^{def} ± 33.6	11.2 ± 16.2

BAL; bronchoalveolar lavage, Mac; macrophages, Lym; lymphocytes, Neut; neutrophils, Eos; eosinophils. S+; patients with glucocorticoid therapy, S-; patients without glucocorticoid therapy. a and g; *p*<0.02, b, d, and e; *p*<0.001, c, f and h; *p*<0.05.

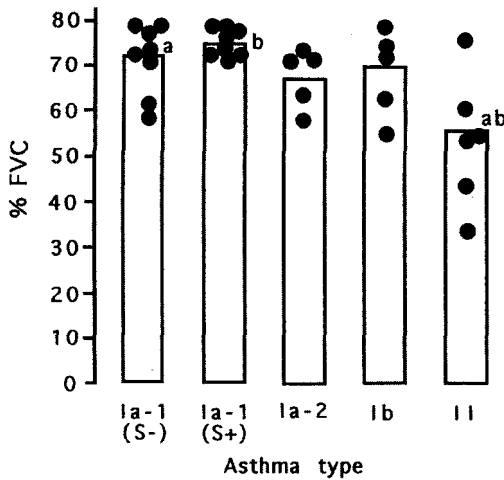


Figure 2. %FVC in patients with asthma classified by clinical symptoms. a;p<0.02, b;p<0.01.

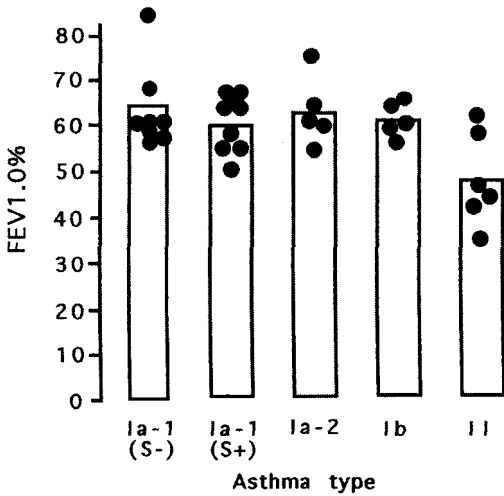


Figure 3. FEV1.0% in patients with asthma classified by clinical symptoms.

and after the treatment (complex spa therapy (17, 18)). The FVC value tended to increase after the treatment in all groups classified by clinical symptoms. A significant increase in FVC after the treatment was found in patients with type Ia-1 (S-; p<0.001, S+; p<0.02), Ia-2 (p<0.02), and Ib (p<0.001). However, the increase in FVC after the treatment was not significant

in patients with type II (Fig.4).

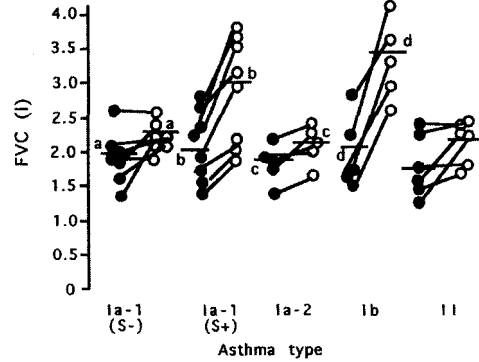


Figure 4. FVC values before (●) and after treatment (○) in patients with asthma classified by clinical symptoms. S+; patients with glucocorticoid therapy, S-; patients without glucocorticoid therapy. a and d; p<0.001, b and c; p<0.02.

A significant increase in FEV1.0 after the treatment was observed in patients with type Ia-1 (S-)(p<0.05) and Ib (p<0.05). However, in the other asthma types, a significant difference was not present between the values in FEV1.0 before and after the treatment (Fig.5).

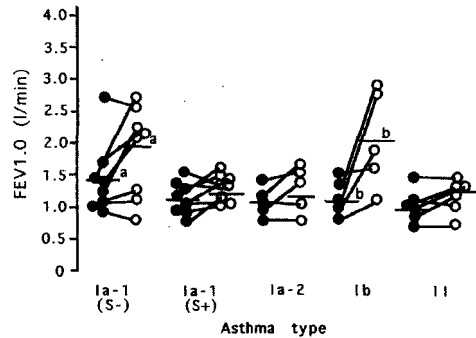


Figure 5. FEV1.0 values before (●) and after treatment (○) in patients with asthma classified by clinical symptoms. S+; patients with glucocorticoid therapy, S-; patients without glucocorticoid therapy. a; p<0.05, b; p<0.05.

Discussion

Bronchial inhalation challenge with allergen causes acute bronchoconstriction and late asthmatic reactions (1-3). Allergen-induced airway narrowing is usually evaluated by a 20% fall of FEV1.0. However, recent studies by Gibbons et al. demonstrate that measure of a 20% fall in FEV1.0 during allergen-induced asthmatic reactions does not evaluate excessive bronchoconstriction, which is the most important abnormality in asthma, since it puts patients at risk for serious illness (22). They suggest that a fall in FVC reflects excessive airway narrowing, which is an important determinant of asthma severity. Thus, they recommend that measuring %fall in FVC when FEV1.0 falls by 20% is a safe method of detecting excessive bronchoconstriction. Patients with greater fall in FVC during bronchial challenge test are more likely to have exacerbations than those with relatively smaller falls in FVC. Our results also show that patients with a greater decrease in %FVC have more severe asthma, often requiring systemic glucocorticoid therapy, than those with smaller fall in %FVC. In fact, 24 (75.0%) of the 32 patients with a low %FVC had SDIA.

When airway smooth muscle contraction produces unlimited bronchoconstriction to the extent that airway closure occurs, this results in an increase in residual volume (RV) with a corresponding decrease in vital capacity (VC). It has been shown that RV increases (23, 24) and VC falls (25) significantly in asthma patients during allergen-induced bronchoconstriction.

It has been clinically observed that many of patients with asthma show a predominant fall in FEV1.0/FVC, whereas some of them show a predominant fall in FVC. In this study, association between decrease in %FVC and clinical asthma types related to airway inflammation was examined in asthmatics whose %FVC was under 80%. A decrease in %FVC was not related to patient age, suggesting that decrease in %FVC is not due to aging. In clinical types of asthma, %FVC value was significantly lower in patients with

type II asthma, in which the proportion of BAL neutrophils was markedly increased, than in those with type Ia-1 and type Ib.

The decreased value of %FVC showed a tendency to increase after the treatment including complex spa therapy (17,18). A significant increase in FVC was observed after the treatment in patients with type Ia-1, Ia-2 and Ib. However, the FVC value in patients with type II did not increase significantly after the treatment compared to the value before the treatment. In contrast, the value of FEV1.0 was significantly improved after the treatment only in patients with type Ia-1(S-). These results demonstrate that a decrease in %FVC in patients with asthma is related to disease severity. The results also suggest that improvement of decreased %FVC value after the treatment is associated with airway inflammation; a significant improvement of FVC was found in type Ib asthma accompanied with BAL eosinophilia, but not in type II asthma with BAL neutrophilia.

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気管支喘息患者における努力肺活量 (%FVC) の低下と気道炎症ならびに臨床病型との関連

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努力肺活量 (%FVC) 低値を示す気管支喘息の臨床病態を明らかにするために気道炎症ならびに臨床病型との関連について検討を行った。%FVC が 80% 未満の気管支喘息患者 32 名を対象として、

スパイロメトリー, 気管支肺胞洗浄 (BAL) を施行し, 臨床病態を解析し, 治療効果の評価を行なった。

1. 対象中 24 名 (75%) の患者がステロイド依存性重症難治性喘息であった。2. 細気管支閉塞型喘息患者において, %FVC 値の有意の低下が認められ, BAL 液中のリンパ球の減少と好中球の増加が認められた。3. FVC 値, FEV1.0 値の治療による改善は, BAL 液中好酸球の増加を示す過分泌型喘息においては認められたが, BAL 液中好中球の増加を示す細気管支閉塞型喘息においては認められなかった。

以上より喘息患者における %FVC 値の低下は気道炎症と関連しており, 細気管支閉塞型喘息における治療による可逆性は著しく低下していることが示唆された。