Peak Expiratory Flow Variability Adjusted by Forced Expiratory Volume in One Second is a Good Index for Airway Responsiveness in Asthmatics

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Abstract

Background The lowest peak expiratory flow (PEF) over a week, expressed as a percentage of the highest PEF (Min%Max PEF) has been reported to be the index that most closely correlates with airway hyperresponsiveness (AHR) in asthmatics. However, both fluctuation of the airway caliber and airflow limitation are regarded as physiological properties of asthma closely related to AHR. An accurate index that shows the degree of AHR may be obtained by combining the index of airway lability with the parameters that represent airway caliber.

Methods Ninety-two steroid-naïve and twenty-eight steroid-treated asthmatic patients were enrolled. Using the physiological parameters obtained from spirometry and PEF monitoring, we investigated the indices which correlate accurately with airway responsiveness measured by the inhalation challenge test.

Results Although the methacholine threshold was related to all parameters that represent airway caliber and lability, Min%Max PEF had the strongest correlation with AHR. When Min%Max PEF was adjusted by the airway geometric factors, the normalization of Min%Max PEF with forced expiratory volume in one second as a percentage of the predicted value (%FEV₁) improved the relationship between Min%Max PEF and AHR.

Conclusions Min%Max PEF adjusted by %FEV₁ showed a good correlation with airway responsiveness measured by the inhalation challenge test, and may be useful as a convenient alternative index of AHR in asthmatic patients

Key words: airway hyperresponsiveness, airway lability, airflow limitation, bronchial asthma, spirometry

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Introduction

Airway hyperresponsiveness (AHR), the degree of airway responsiveness to various nonspecific stimuli, is an important physiological feature of asthma (1-3). It has been reported that evaluation of AHR is useful to diagnose asthma (1, 2), assess the response to asthma therapy (4-6), and guide asthma treatment (7, 8). However, the standard method of assessing AHR, inhalation challenge test, is not easy to perform in clinical practice.

Although multiple factors are involved in the mechanism of AHR, both fluctuation of the airway caliber and airflow limitation are regarded as physiological properties of asthma closely related to AHR (3, 4, 9-14). Peak expiratory flow (PEF) monitoring is accepted as a part of asthma management that provides information about fluctuations of the airway caliber, known as airway lability (1). Among several PEF indices, the lowest PEF over a week, expressed as a percentage of the highest PEF (Min%Max PEF) has been suggested to be the best index of airway lability in clinical practice because it more strongly correlates with AHR than

Table 1. Subject Demographics

	Steroid-naïve	Steroid-treated
Number	92 (F/M = 57/35)	28 (F/M = 15/13)
Asthma status	Mild persistent = 58 Moderate persistent = 34	Controlled = 25 Partly controlled = 3
Age (Years)	45.7 ± 1.7	41.1 ± 1.9
FVC (L)	3.28 ± 0.08	3.56 ± 0.14
FEV ₁ (L)	2.54 ± 0.08	2.85 ± 0.11
FEV ₁ % (%)	77.2 ± 0.1	80.5 ± 1.6
%FEV ₁ (%)	91.0 ± 1.2	92.4 ± 1.7
Rrs (cmH ₂ O/L/s)	4.3 ± 0.1	4.6 ± 0.3
Min PEF (L/min)	342 ± 12	379 ± 21
Max PEF (L/min)	410 ± 12	442 ± 22
Mean PEF (L/min)	376 ± 12	410 ± 22
Min%Max PEF (%)	82.8 ± 0.8	85.3 ± 1.1
PD ₂₀₀ (mg/mL)	14.0 ± 2.1	16.6 ± 1.7

Definition of abbreviations: F: female, M: male, FVC: forced vital capacity, FEV₁: forced expiratory volume in one second, %FEV₁: FEV₁ expressed as a percentage of the predicted value, Rrs: respiratory resistance, PEF: peak expiratory flow, Min PEF: the lowest PEF over a week, Max PEF: the highest PEF over a week, Mean PEF: the mean value of the lowest and highest PEF, Min%Max PEF: the lowest PEF over a week, expressed as the percentage of the highest PEF, PD₂₀₀: cumulative provocative dose of methacholine causing a 100% increase in respiratory resistance. Values are mean ± SE.

any other physiological parameters (12). However, a close association was also found between lower level parameters that represent airway caliber such as forced expiratory volume in one second (FEV₁) and AHR (3, 4, 9, 10). Therefore, we hypothesized that an accurate index that shows the degree of AHR may be obtained by combining the index of airway lability with the parameters that represent airway caliber.

In the current study, using the physiological parameters obtained from spirometry and PEF monitoring, we investigated the indices which correlate accurately with AHR measured by the inhalation challenge test in patients with asthma.

Methods

Study subjects

Ninety-two steroid-naïve and twenty-eight steroid-treated, nonsmoking asthmatic patients took part in the study after giving informed consent. The study was approved by the local ethics committee. All patients satisfied the American Thoracic Society criteria for asthma (15). The clinical characteristics of the study subjects are shown in Table 1. All patients in the steroid-naïve group attended our outpatient clinic recently, and had been without regular asthma treatment including steroid therapy. The asthma severity was classified in fifty-eight subjects as mildly persistent, and in thirty-four as moderately persistent (1). The patients in the steroid-treated group had been treated with inhaled corticosteroids at a mean equivalent dose of 372 µg fluticasone propionate·day⁻¹ without any other regular asthma treatment.

The asthma control levels of twenty-five steroid-treated patients were classified as controlled, but three patients were classified as partly controlled because their FEV₁ value were below 80% of the predicted values (1). Rescue use of short acting inhaled β₂ agonists as needed for relief of symptoms was permitted. Because of safety concerns with methacholine challenge testing, steroid-naïve subjects whose asthma severity was classified as severe persistent, steroid-treated patients whose control level was classified as uncontrolled, and subjects with impaired lung function (FEV₁ < 55% predicted value) were not enrolled in this study. In addition, subjects were not included if they had had an exacerbation of asthma, or a respiratory tract infection, in the two weeks preceding the study, or the use of rescue inhaled β₂ agonists within twenty-four hours before the inhalation challenge test.

Study design

The present study was cross-sectional. Subjects attended the outpatient clinic at the Wakayama Medical University hospital on one occasion for clinic examination, spirometry, and methacholine inhalation challenge. PEF monitoring was performed for at least two weeks before this attendance.

Methacholine inhalation challenge test

Airway responsiveness was measured using a device (Astograph Jupiter 21; Chest Co., Tokyo, Japan) that displays respiratory resistance (Rrs) measured via the forced oscillation method during tidal breathing with continuous inhalation of the aerosolized methacholine as previously described (16). The degree of the airway responsiveness was defined as the cumulative provocative dose of methacholine causing

Table 2. Correlation between Airway Responsiveness to Methacholine and Airway Physiologic Parameters

Physiologic parameters	Coefficient	p value	95% CI
Rrs (cmH ₂ O/L/s)	-0.461	< 0.0001	-0.591 , -0.307
FVC (L)	0.287	< 0.005	0.113 , 0.443
FEV ₁ (L)	0.408	< 0.0001	0.246 , 0.547
%FEV ₁ (%)	0.607	< 0.0001	0.480 , 0.709
Min PEF (L/min)	0.449	< 0.0001	0.293 , 0.581
Max PEF (L/min)	0.297	< 0.001	0.124 , 0.452
Mean PEF (L/min)	0.374	< 0.0001	0.209 , 0.519
Min%Max PEF (%)	0.709	< 0.0001	0.607 , 0.788

Definition of abbreviations: CI: confidence interval, Rrs: respiratory resistance, FVC: forced vital capacity, FEV₁: forced expiratory volume in one second, %FEV₁: FEV₁ expressed as a percentage of the predicted value, PEF: peak expiratory flow, Min PEF: the lowest PEF over a week, Max PEF: the highest PEF over a week, Mean PEF: the mean value of the lowest and highest PEF, Min%Max PEF: the lowest PEF over a week, expressed as the percentage of the highest PEF

a 100% increase in baseline Rrs (PD₂₀₀) (17).

Pulmonary function test

FEV₁ and forced vital capacity (FVC) were measured with a Chest HI 801 (Chest Co., Tokyo, Japan) according to the standard procedure (18).

PEF measurements

Using an Assess[®] peak flow meter (Respironics Health Scan Inc., Cedar Grove, NJ, USA), PEF measurements were performed twice a day for at least two weeks according to the standard procedure (19). The lowest PEF expressed as a percentage of the highest PEF in the previous week before the methacholine inhalation challenge test was assumed to represent the PEF variability for the week (Min%Max PEF) (1, 12).

Adjustment of PEF variability for physiological parameters that represent airway caliber

To investigate the physiological indices which correlate accurately with AHR in asthmatics, Min%Max PEF was adjusted by several airway geometric factors. Seven separate indices were calculated as follows:

1. Min%Max PEF adjusted by Rrs

The Min%Max PEF was divided by the actual Rrs value.

2. Min%Max PEF adjusted by FVC

The Min%Max PEF was multiplied by the actual FVC value.

3. Min%Max PEF adjusted by FEV₁

The Min%Max PEF was multiplied by the actual FEV₁ value.

4. Min%Max PEF adjusted by %FEV₁

The Min%Max PEF was multiplied by the FEV₁ percentage of the predicted value (%FEV₁).

5. Min%Max PEF adjusted by Minimum PEF

The Min%Max PEF was multiplied by the actual lowest PEF value during one week.

6. Min%Max PEF adjusted by Maximal PEF

The Min%Max PEF was multiplied by the actual highest

PEF value during one week.

7. Min%Max PEF adjusted by Maximal PEF

The Min%Max PEF was multiplied by the actual mean value of the lowest and highest PEF during one week.

Statistical analysis

Spearman's correlation coefficients were calculated to determine the correlation between the methacholine threshold and pulmonary physiological parameters. All data were expressed as means $\pm$ SE, and significance was defined as a p value of less than 0.05.

Results

Correlation between airway physiological parameters and airway responsiveness

The results of the correlation coefficient analysis between the airway responsiveness and airway physiologic parameters are listed in Table 2. Although the PD₂₀₀ was related to all parameters that represent airway caliber and lability (Table 2 and Fig. 1), Min%Max PEF had the strongest correlation with AHR ($r=0.709$, $p<0.0001$) (Table 2 and Fig. 2A).

Impact of adjusting the PEF variability for airway caliber on the correlation with AHR

When Min%Max PEF was adjusted for airway geometric factors, the normalization with %FEV₁ improved the correlation between Min%Max PEF and AHR ($r=0.750$, $p<0.0001$) (Table 3 and Fig. 2B). By contrast, other geometric factors such as actual FEV₁ and Rrs values did not improve the relationship between Min%Max PEF and airway responsiveness (Table 3). A nomogram incorporating Min%MaxPEF with %FEV₁ was constructed to predict the degree of airway responsiveness measured by the methacholine challenge test (Fig. 3). The PD₂₀₀ value was calculated by the correlation equation obtained from regression analysis, as follows: $\log PD_{200} = \text{Min\%Max PEF} \times \%FEV_1 / 1885 - 2.9$.

Figure 1. Relationship between airway responsiveness to methacholine and physiological parameters that represent airway caliber: a) respiratory resistance value; b) actual forced volume in one second (FEV_1) value; c) FEV_1 percentage of the predicted value ($\%FEV_1$); d) the lowest peak expiratory flow (PEF) value during one week; e) the highest PEF value during one week; f) mean value of the lowest and highest PEF value. The lines correspond to the fitted regression equation.

Discussion

In the current study, the correlation coefficient analysis indicated that airway responsiveness measured by the inhalation challenge test correlated with the parameters that represent airway caliber and lability, and Min%Max PEF had the strongest correlation with AHR in asthmatics. However, the normalization of Min%Max PEF with $\%FEV_1$ improved the relationship between Min%Max PEF and AHR.

AHR is a consistent and defining feature of asthma (1-3). AHR measurement is a valuable tool in the diagnosis of asthma (1, 2), and for evaluating the treatment response (4-6). In addition, it has been demonstrated that asthma management plans that include AHR measurements are superior to plans without AHR measurements (7, 8). Although airway responsiveness is generally evaluated by inhalation challenge test using bronchoconstrictive agents, it is not convenient and involves several clinical issues such as inva-

siveness and contraindications (2). Therefore, establishing a convenient index for predicting the degree of airway responsiveness other than by using the inhalation challenge test would be useful for clinical asthma management.

Several mechanisms, such as airway inflammation, increased neural reflexes, airway geometric factors, and genetic factors, have been proposed to explain the AHR (1-4). Among these mechanisms, airway inflammation has been reported to be a key factor (3, 4, 6, 7), and it also affects the other important physiologic properties of asthma, such as airflow limitation and airway lability (3, 4, 6). Previous studies have shown close correlations between PEF variability and AHR (11-14). In particular, Reddel et al recommended Min%Max PEF as the best index of airway lability in clinical practice (12). However, a reduction in airway caliber would result in a greater increase in airway resistance and consequently greater airflow limitation (20), and a close association was found between lower level parameters that represent airway caliber such as FEV_1 and AHR (3, 4,

Table 3. Correlation between Airway Responsiveness to Methacholine and Indices that Variability of Peak Expiratory Flow Adjusted by Airway Geometric Factors

Adjusting factors	Coefficient	p value	95% CI
Not adjusted	0.709	< 0.0001	0.607 , 0.788
Rrs (cmH ₂ O/L/s)	0.577	< 0.0001	0.444 , 0.686
FVC (L)	0.473	< 0.0001	0.322 , 0.602
FEV ₁ (L)	0.532	< 0.0001	0.390 , 0.649
%FEV ₁ (%)	0.750	< 0.0001	0.659 , 0.819
Min PEF (L/min)	0.538	< 0.0001	0.398 , 0.654
Max PEF (L/min)	0.449	< 0.0001	0.293 , 0.581
Mean PEF (L/min)	0.495	< 0.0001	0.347 , 0.619

Definition of abbreviations: CI: confidence interval, Rrs: respiratory resistance, FVC: forced vital capacity, FEV₁: forced expiratory volume in one second, %FEV₁: FEV₁ expressed as a percentage of the predicted value, PEF: peak expiratory flow, Min PEF: the lowest PEF over a week, Max PEF: the highest PEF over a week, Mean PEF: the mean value of the lowest and highest PEF, Min%Max PEF: the lowest PEF over a week, expressed as the percentage of the highest PEF

Figure 2. Relationship between airway responsiveness and the lowest peak expiratory flow (PEF) during one week expressed as a percentage of the highest PEF (Min%Max PEF) normalized with or without forced volume in one second (FEV₁) percentage of the predicted value (%FEV₁): a) Min%Max PEF; b) Min%Max PEF adjusted by %FEV₁. The lines correspond to the fitted regression equation.

9, 10). Therefore, we sought to investigate the indices which correlate accurately with AHR by combining the index of airway lability with the parameters that represent airway caliber.

In fact, the current study demonstrated that %FEV₁ was the airway geometric factor that correlated well with AHR,

Figure 3. The nomogram to predict the degree of airway responsiveness in asthmatic subjects incorporating the variability of peak expiratory flow (Min%Max PEF) and forced expiratory volume in one second percentage of the predicted value (%FEV₁). A cumulative provocative dose of methacholine causing a 100% increase in respiratory resistance (PD₂₀₀) was calculated by a correlation equation obtained from the regression analysis, as follows: $\log PD_{200} = \text{Min\%Max PEF} \times \%FEV_1 / 1885 - 2.9$.

and adjusting Min%Max PEF for %FEV₁ improved the correlation between Min%Max PEF and AHR. Airflow limitation in subjects with asthma may be reversible or fixed, and appears to represent a different dimension of asthma severity from airway lability. Several previous studies have shown that airflow limitation can be present with normal PEF variability and severe AHR (21-24). In addition, PEF measurements can underestimate the degree of airflow limitation, particularly as airflow limitation and gas trapping worsen (1). These are possible explanations for the fact that adjust-

ing the PEF variability for %FEV₁ improved the relationship between Min%Max PEF and AHR. Actually, the improvement of this relationship by adjusting it by %FEV₁ seemed to be more remarkable in the cases with higher airway responsiveness. By contrast, other geometric factors such as actual FEV₁ and Rrs values had significant but weak correlations with the methacholine threshold, and consequently the normalization of Min%Max PEF with these geometric factors did not improve the relationship between Min%Max PEF and AHR.

Min%Max PEF adjusted by %FEV₁ appeared to be a convenient alternative to the index of AHR in asthmatic patients, and the resulting nomogram that could predict the degree of airway responsiveness may be useful for clinical asthma management. Because this proposed index correlated accurately with the degree of AHR, and it could be obtained by using conventional airway physiological parameters measured by spirometry and PEF monitoring. However, pre-

cise instruction is necessary so that patients can reliably measure PEF (1). In addition, although it has been demonstrated that PEF variability is the most useful index for reflecting AHR longitudinally in treated asthmatic patients, its correlations are not very strong (13). Thus, a longitudinal validation study is needed to clarify the utility of adjusting the measurements of Min%Max PEF by %FEV₁ as a clinical index for the changes in AHR by pharmacologic interventions for asthma.

In conclusion, Min%Max PEF adjusted by %FEV₁ showed a good correlation with the airway responsiveness measured by the inhalation challenge test, and may serve as a convenient alternative to the index of AHR in asthmatic patients.

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