Relationship between Small Airway Function and Health Status, Dyspnea and Disease Control in Asthma

Tomoshi Takeda^a Toru Oga^b Akio Niimi^a Hisako Matsumoto^a Isao Ito^a
Masafumi Yamaguchi^a Hirofumi Matsuoka^a Makiko Jinnai^a Kojiro Otsuka^a
Tsuyoshi Oguma^a Hitoshi Nakaji^a Kazuo Chin^b Michiaki Mishima^a

Departments of ^aRespiratory Medicine, and ^bRespiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Key Words

Asthma · Dyspnea · Impulse oscillometry · Peripheral airways · Spirometry

Abstract

Background: Small airways play important roles in the pathophysiology of asthma. However, relationships between small airway involvement and health status and dyspnea have not been investigated. **Objectives:** It was the aim of this study to assess the relationships between proximal and peripheral airway functions and health status, dyspnea and disease control in patients with asthma, using impulse oscillometry (IOS). **Methods:** We performed IOS, spirometry and assessment of health status (Asthma Quality of Life Questionnaire and St. George's Respiratory Questionnaire), dyspnea (Baseline Dyspnea Index) and disease control (Asthma Control Questionnaire) in 65 asthmatics and evaluated their relationships. **Results:** Peripheral airway function as evaluated by IOS [R5–R20 (the fall in resistance from 5 to 20 Hz) and X5 (reactance at 5 Hz)], in addition to the proximal airway index (R20), significantly correlated with health status, dyspnea and disease control. Multiple regression analyses revealed that peripheral airway function significantly

contributes to these, independently of the proximal airway index. In contrast, forced expiratory volume in 1 s did not significantly contribute to health status or dyspnea. **Conclusions:** IOS correlated better with clinical symptoms and asthma control than spirometry in patients with asthma. Peripheral and proximal airway functions as assessed separately by IOS independently contribute to health status, dyspnea and disease control, indicating that peripheral airways also represent an important therapeutic target.

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Introduction

Health status (health-related quality of life) and dyspnea are important clinical outcomes in asthma. These patient-reported outcomes imply functional impairments that are important to asthma patients during everyday life [1, 2]. Although asthma is characterized by variable airflow limitation, health status and dyspnea are often only weakly correlated with the forced expiratory volume

Toru Oga and Akio Niimi contributed equally to this article.

in 1 s (FEV_1), the gold standard for the assessment of air-flow limitation, and are considered to be measured independently of clinical physiological measurements [1, 2].

Autopsy studies of patients dying from asthma have shown that inflammation and remodeling involve both large and small airways [3, 4]. Increasing evidence indicates that inflammation of peripheral airways plays an important role in the pathophysiology of asthma [5–7]. Therefore, significant effects of peripheral airways on health status and dyspnea are expected in asthma, but the issue remains unclear, probably due to methodological difficulties in evaluating peripheral airways. Strong correlations between FEV_1 and health status and dyspnea may be lacking because FEV_1 mainly reflects expiratory flow at high and middle lung volumes, and thus, cannot provide accurate or specific information on peripheral airways. Forced expiratory flow technique may not be appropriate for assessing peripheral airways, as forced expiratory flow rates at mid-to-low lung volumes exhibit marked variability and may be affected by changes in proximal airway patency and lung volumes [8].

Recently, impulse oscillometry (IOS) has been utilized as a simple and noninvasive method of assessing pulmonary function without forced maneuvers in the investigations of asthma and chronic obstructive pulmonary disease [9–12]. IOS can separately quantify the degree of proximal and peripheral airway abnormalities, and thus, has been increasingly used in both adults [13–16] and children [17, 18].

We hypothesized that significant relationships would exist between peripheral airway function and both health status and dyspnea in patients with asthma, and that this could be detected using IOS. Therefore, the present cross-sectional study examined interrelationships between pulmonary function as assessed by IOS and spirometry, and patient-reported outcomes of health status, dyspnea and disease control.

Materials and Methods

Subjects

Subjects comprised 65 consecutive outpatients with clinically stable asthma at Kyoto University Hospital asthma clinic. Entry criteria for the study were as follows: (1) meeting the definition of asthma by the American Thoracic Society [19]; (2) confirmation of airway hyperresponsiveness [20–22] on past evaluations; (3) never smokers or ex-smokers who had smoked <5 pack-years but had not smoked for >1 year [20]; (4) regular attendance at our clinic for >3 months; (5) no exacerbation of asthma over the last 4 weeks; (6) no changes in treatment within 4 weeks, and (7) no evidence of chronic obstructive pulmonary disease or other respi-

ratory diseases. All subjects finished the following examinations between 9 and 12 a.m. on the same day, including IOS followed by spirometry and assessment of health status, dyspnea and asthma control. The research protocol was approved by the ethics committee of Kyoto University.

Outcome Measures

Health Status. Health status was assessed using the Japanese versions of the standardized version of the Asthma Quality of Life Questionnaire (AQLQ) [23] and the St. George's Respiratory Questionnaire (SGRQ) [24, 25]. One of the authors (T.T.) reviewed the survey to ensure that subjects did not unintentionally omit any questions.

The AQLQ consists of 32 items comprising 4 domains: symptoms (12 items), activity limitations (11 items), emotional function (5 items) and exposure to environmental stimuli (4 items). The present study used the self-administered version. Patients were asked to recall their experiences during the previous 2 weeks and to score each item using a 7-point scale (1 = maximal impairment, 7 = no impairment). Domain scores were calculated as the mean score from the items forming each domain, and the overall score was calculated as the mean of the sum of all items.

The SGRQ comprises 50 items divided into 3 components: symptoms (8 items), activity (16 items) and impacts (26 items). The total score was also calculated from all component items. SGRQ scores ranged from 0 to 100 (0 = best health, 100 = worst health).

Dyspnea. Dyspnea during daily activities was evaluated using the Japanese version of the Baseline Dyspnea Index (BDI) [26, 27], which was developed as a discriminative instrument to measure dyspnea at a single point in time in various respiratory diseases, including asthma [28]. The BDI recognizes 5 grades from 0 (severe) to 4 (not impaired) for each of the following 3 categories: functional impairment, magnitude of task and magnitude of effort. The total BDI score was calculated as the sum of these 3 categories.

Asthma Control. To measure asthma control, the Japanese version of the Asthma Control Questionnaire (ACQ) [29] was used. This questionnaire examines 5 symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze), a question about rescue β_2 -agonist use and another about FEV_1 , with this last question completed by clinic staff. Patients recall their experiences during the previous 7 days and respond to each question using a 7-point scale. The items are equally weighted and the ACQ score is given as the mean of the 7 items and is therefore between 0 (well controlled) and 6 (extremely poorly controlled).

Spirometry. Subjects underwent spirometric testing according to the recommended method [30], using a ChestGraph HI-701 spirometer (Chest, Tokyo, Japan). Pre-bronchodilator values of FEV_1 were examined.

Impulse Oscillometry. Measurement of respiratory impedance by IOS was conducted using an oscillatory system (MS-IOS; Erich Jaeger, Hoechberg, Germany), fulfilling standard recommendations [9]. In short, rectangular mechanical impulses containing the whole frequency spectrum were applied to the respiratory system through a mouthpiece while the patient was breathing quietly. The resulting pressure and flow signals were analyzed for amplitude and phase differences to determine resistance (R) and reactance (X) of the total respiratory system. Impedance measurements included resistance from 5 to 35 Hz (R5–R35), reac-

Table 1. Characteristics of 65 patients with asthma

Gender, female/male	37/28
Age, years	55.2 ± 17.4
Severity of asthma, step 1/2/3/4	7/20/28/10
Medication	
Inhaled corticosteroids, administered/not administered	58/7
Doses of inhaled corticosteroids ¹ , µg/day	395 ± 239
Long-acting β ₂ -agonists, administered/not administered	29/36
Leukotriene modifiers, administered/not administered	20/45
Theophylline, administered/not administered	8/57
FEV ₁ , liters	2.27 ± 0.97
FEV ₁ , % predicted	88.7 ± 20.8
R20, kPa s l ⁻¹	0.33 ± 0.12
R5–R20, kPa s l ⁻¹	0.086 ± 0.141
X5, kPa s l ⁻¹	–0.174 ± 0.228
AQLQ overall (1–7)	5.57 ± 1.15
SGRQ total (0–100)	27.0 ± 20.0
BDI (0–12)	9.8 ± 2.1
ACQ (0–6)	1.04 ± 1.01

Numbers in parentheses indicate theoretical score ranges.
¹ Doses of inhaled corticosteroids were converted into the equivalent dose of fluticasone propionate.

tance from 5 to 35 Hz (X5–X35) and frequency of resonance, which represents the point at which the usually negative reactance reaches 0, measured in Hertz. In the present study, we used respiratory resistance at 5 and 20 Hz (R5 and R20) as indices of total and proximal airway resistance, respectively, and considered the fall in resistance from 5 to 20 Hz (R5–R20) as a surrogate for the resistance of peripheral airways, as reported previously [10, 12, 16, 17, 31, 32]. Moreover, reactance at 5 Hz (X5), which may be determined by homogenous distribution of ventilation, effective ventilation capacity, and compliance of the lung and chest wall, was also considered representative of peripheral airway abnormalities such as those caused by inflammation [10, 12, 17, 33].

Statistical Analysis

Results are expressed as means ± standard deviation. Relationships between different outcome measurements were analyzed using Pearson's correlation coefficient tests. For ordinal variables such as the BDI, we performed additional correlations using Spearman's rank correlation coefficient tests to confirm that values for these correlations were compatible with Pearson's correlation coefficients. We then chose to present all results as Pearson's correlation coefficients for ease of comprehension and comparison across relationships [28]. Forward and backward stepwise multiple regression analyses were performed to identify variables that could best predict health status, dyspnea and disease control, using pulmonary function indices and medications as independent variables. Independent variables including the daily doses of inhaled corticosteroids were used as continuous variables, except that the categorical variables such as use of long-acting β₂-agonists, leukotriene modifiers and theophylline were coded as 1 (administered) or 0 (not administered) for the analysis. Values of $p < 0.05$ were considered statistically significant.

Results

Subject characteristics are presented in table 1. Among the 65 patients, 58 had never smoked. Severity of asthma was intermittent (step 1) in 7 patients, mild persistent (step 2) in 20, moderate persistent (step 3) in 28, and severe persistent (step 4) in 10, based on the classification according to the Global Initiative for Asthma guidelines [34].

Table 2 shows correlation coefficients between health status, dyspnea and disease control and pulmonary function and medications. Regarding health status, the overall score for the AQLQ and the total score for the SGRQ significantly but weakly correlated with FEV₁ (correlation coefficient, $r = 0.33$ and 0.35), moderately correlated with R20 ($r = 0.54$ and 0.51), R5–R20 ($r = 0.50$ and 0.50) and X5 ($r = 0.49$ and 0.48), and weakly to moderately correlated with dose of inhaled corticosteroid and administration of theophylline ($r = 0.35$ – 0.41). Regarding dyspnea, the BDI moderately correlated with FEV₁, R20, R5–R20 and X5 ($r = 0.41$ – 0.57) and weakly correlated with administration of theophylline ($r = 0.32$). Regarding disease control, the ACQ score moderately correlated with FEV₁, R20, R5–R20 and X5 ($r = 0.43$ – 0.55), and weakly to moderately correlated with dose of inhaled corticosteroid and administration of long-acting β₂-agonists, leukotriene modifiers and theophylline ($r = 0.28$ – 0.46).

Table 2. Correlation coefficients between pulmonary function and medications and health status, dyspnea and disease control

	AQLQ overall	SGRQ total	BDI	ACQ
FEV ₁	0.33	-0.35	0.41	-0.55
R20	-0.54	0.51	-0.49	0.43
R5-R20	-0.50	0.50	-0.57	0.55
X5	0.49	-0.48	0.54	-0.53
Daily doses of inhaled corticosteroids ^a	-0.36	0.35	-	0.42
Use of long-acting β_2 -agonists ^b	-	0.31	-	0.28
Use of leukotriene modifiers ^b	-	-	-	0.33
Use of theophylline ^b	-0.35	0.41	-0.32	0.46

Missing data (-) indicate that no statistically significant relationships were identified.

^a Doses of inhaled corticosteroids were converted into the equivalent dose of fluticasone propionate.

^b Use of long-acting β_2 -agonists, leukotriene modifiers or theophylline was coded as 1 (administered) or 0 (not administered) for the analysis.

Table 3. Results of stepwise multiple regression analyses to predict health status, dyspnea and disease control

Independent variables	AQLQ overall	SGRQ total	BDI	ACQ
FEV ₁	-	-	-	0.19
R20	0.21	0.18	0.13	-
R5-R20	-	0.11	0.24	-
X5	0.12	-	-	0.16
Daily doses of inhaled corticosteroids ^a	0.10	-	-	-
Use of long-acting β_2 -agonists ^b	-	0.07	-	-
Use of leukotriene modifiers ^b	-	-	-	-
Use of theophylline ^b	-	0.10	-	0.12
Cumulative r ²	0.43	0.46	0.37	0.47

Missing data (-) indicate that independent variables were not statistically significant. All values represent the coefficient of determination (r²).

^a Doses of inhaled corticosteroids were converted into the equivalent dose of fluticasone propionate.

^b Use of long-acting β_2 -agonists, leukotriene modifiers or theophylline was coded as 1 (administered) or 0 (not administered) for the analysis.

Table 3 shows the results of stepwise multiple regression analyses performed to identify which variables of pulmonary function or medications could predict health status, dyspnea and disease control. Regarding health status, R20, X5 and dose of inhaled corticosteroid significantly accounted for the AQLQ (r² = 0.21, 0.12 and 0.10, respectively). R20, R5-R20 and administration of theophylline and long-acting β_2 -agonists significantly accounted for the SGRQ (r² = 0.18, 0.11, 0.10 and 0.07, respectively). Regarding dyspnea, R20 and R5-R20 significantly explained the BDI (r² = 0.13 and 0.24, respectively).

Regarding disease control, FEV₁, X5 and administration of theophylline significantly accounted for the ACQ score (r² = 0.19, 0.16 and 0.12, respectively).

Discussion

We assessed relationships between proximal and peripheral airway function and health status, dyspnea and disease control of patients with asthma, using the different instruments of IOS and spirometry. We demonstrat-

ed that peripheral airway function (R5–R20 and X5), in addition to proximal airway function (R20), as evaluated by IOS, correlated significantly with health status, dyspnea and disease control. In multiple regression analyses, peripheral airway function contributed significantly to these parameters, independent of proximal airway function (R20). In contrast, the index of spirometry (FEV₁) did not significantly contribute to health status or dyspnea by multiple regression analyses, unlike the indices of IOS.

In the present study, peripheral airway function as evaluated by R5–R20 or X5 in addition to proximal airway function evaluated by R20 moderately correlated with the AQLQ, SGRQ and BDI. A number of previous studies have indicated only weak correlations between these health status and dyspnea measurements, and airflow limitation evaluated by FEV₁ [1, 2], which may preferentially reflect obstruction of proximal airways. Using the IOS technique, we have demonstrated significant correlations between peripheral airway dysfunction and both health status and dyspnea. The importance of peripheral airways in asthma has been well recognized. Peripheral airway disease has been associated with airway hyperresponsiveness [5, 20, 35], nocturnal asthma [5, 36], exacerbation of asthma [5, 37], severe asthma [5, 20, 38], increased asthma symptoms [39], exercise-induced asthma [40], and others. Therefore, significant relationships between peripheral airway function on IOS and health status and dyspnea would be understandable. Certainly, the data should be interpreted and discussed keeping in mind the issue of multiple testing and the possibility of type 1 statistical error.

Using multiple regression analyses, peripheral airway dysfunction (R5–R20 or X5) contributed significantly to the AQLQ, SGRQ and BDI, independent of proximal airway dysfunction (R20). The degrees of these contributions were almost equivalent between proximal and peripheral airway indices. To the best of our knowledge, this is the first study to demonstrate a comparative contribution of proximal and peripheral airway abnormalities to health status and dyspnea.

FEV₁ was only weakly correlated with the AQLQ, SGRQ and BDI, as often reported previously [1, 2, 41, 42]. FEV₁ did not significantly contribute to these measures according to multiple regression analyses. Thus, the present study indicates that the status of airways as measured by spirometry does not well reflect the health status or dyspnea in asthma, unlike the case with separate measurements of proximal and peripheral airways by IOS. Two reasons may be taken into consideration. First, as

suggested by Wagner et al. [44], despite the apparent lack of pulmonary impairments assessed by FEV₁ and forced vital capacity, patients with asthma experience significantly increased peripheral airway resistance compared with normal subjects. Forced expiratory maneuvers with spirometry involve deep inspiration, which may affect airway tone. IOS measurements might more accurately reflect changes in airway caliber than spirometry measurements. Second, airflow indices of spirometry may only roughly reflect the presence of airway inflammation [45, 46]. IOS might more precisely reflect such underlying airway inflammation, which may affect deterioration of health status or dyspnea, although this speculation remains yet to be clarified. This supposition could be tested by correlating IOS measures with noninvasive assessment of the alveolar fraction of exhaled nitric oxide or direct invasive determination of inflammatory changes in the distal lung through transbronchial biopsies or peripheral lung brushings.

We have recently reported the usefulness of high-resolution computed tomography in the assessment of small airways in asthma [20]. Other methods to assess peripheral airways include closing volume measurement [37] and the multiple breath washout test [47]. As compared with these methods, IOS is easier and less invasive and time consuming, thus representing a more practical tool to evaluate peripheral airway function [11]. In addition, as demonstrated in the present study, IOS indices reflected patient-reported outcomes better than spirometry, considering the separate effects of proximal and peripheral airway functions. In clinical trials investigating drug effects on asthma, as compared with control drugs, improvements in health status and disease control may be observed even though spirometric indices such as FEV₁ or peak expiratory flow may not be significantly affected [48, 49]. These results may be attributable to treatment effects on peripheral airways, which might have been detected by IOS.

The present study also evaluated the relationship between disease control and pulmonary function and medications. All pulmonary function indices were significantly and moderately correlated with the ACQ, and in multiple regression analyses, X5 and FEV₁ contributed equivalently significantly to the ACQ, indicating the importance of both proximal and peripheral airways on asthma control.

There is also some evidence that IOS is a quantification of both proximal and peripheral airway abnormalities. We have recently shown that in patients with asthma, R20 correlated moderately with peak expiratory flow

and that R5–R20 correlated moderately with mid-forced expiratory flow, residual volume and residual volume/total lung capacity, respectively, supporting the assumption that R20 is a marker of proximal airways, while R5–R20 reflects peripheral airway disease [12]. We have then shown that IOS was useful in detecting the effects of an ultrafine-particle inhaled corticosteroid on peripheral airways compared with a large-particle inhaled corticosteroid [12]. Jain et al. [50] demonstrated that IOS values such as the reversibility of X5 after bronchodilators were significantly correlated with the degree of air trapping as assessed by high-resolution computed tomography, indicating that both measurements reflect peripheral airway abnormalities. Other studies demonstrated that long-acting β_2 -agonists combined with inhaled corticosteroids [13] or oral leukotriene modifiers [17] improved peripheral airway function as well as proximal airway function by using IOS.

In the present study, doses of inhaled corticosteroids or administration of long-acting β_2 -agonists or theophylline significantly accounted for health status or disease control. This may be due to the fact that the dose of in-

haled corticosteroid was increased and other drugs were added based on the severity of disease. Our study was conducted in a cross-sectional fashion, and longitudinal studies should be expected to investigate the effects of those drugs on patient-reported measurements.

The AQLQ and the SGRQ are 2 of the most widely used disease-specific health status instruments in asthma. Both significantly and similarly correlate with global estimates of asthma severity [51] and other important asthma outcomes and have shown high reliability and validity, as well as high levels of responsiveness. We have found that the patterns of contributions of proximal and peripheral airways to the AQLQ and SGRQ are nearly the same.

In conclusion, IOS correlated better with clinical symptoms and asthma control than spirometry in patients with asthma. Both peripheral and proximal airway function as assessed by IOS significantly and independently contributed to health status, dyspnea and disease control in patients with asthma. From the perspective of patient-reported outcomes, peripheral airways also are a potentially important therapeutic target in asthma.

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