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Evaluation of Respiratory Impedance in Asthma and COPD by an Impulse Oscillation System

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Abstract

Objective The purpose of this study was to clarify the differences in physiological properties of the airways between asthma and COPD using an impulse oscillation system (IOS).

Patients and Methods Subjects comprised 95 stable COPD patients, 52 never-smoker asthma patients and 29 healthy never-smokers >60 years old, all matched for age, in whom respiratory impedance was examined by IOS.

Results In both asthma and COPD patients, a significant increase in respiratory resistance (Rrs5) and more negative value of respiratory reactance (Xrs5) at 5 Hz of oscillatory frequency with an increase in resonant frequency (*f*res) were observed when compared with healthy never-smokers. In asthma, a significant increase in respiratory resistance at 20 Hz (Rrs20) was also observed when compared with healthy never-smokers and COPD. The increases in Rrs5 and relative changes of Xrs5 to more negative were remarkable with increasing severity of COPD. On the other hand, among patients with asthma, these changes in Rrs5 and Xrs5 were also observed in asthmatics with normal FEV_1/FVC. Interestingly, Xrs5 showed further changes to more negative in expiration of tidal breath in severe COPD, whereas no significant changes in Xrs5 to more negative in expiration was observed in healthy never-smokers and asthmatics with and without normal FEV_1/FVC.

Conclusion IOS may be useful for detecting pathophysiological changes of respiratory system in accordance with severity of COPD and even in asthmatics with normal FEV_1/FVC. The larger within-breath changes of Xrs5 to more negative in severe COPD may represent easy collapsibility of small airways in expiration of tidal breath. These properties may help to analyze airway mechanics and to identify abnormalities of the airways that cannot be found by spirometry alone.

Key words: asthma, COPD, impulse oscillometry, resistance, reactance, expiratory airflow obstruction

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Introduction

COPD is characterized by not fully reversible airflow limitation, mainly attributable to both narrowing due to airway wall remodeling and the collapsibility in expiration due to loss of alveolar attachment and elastic recoil at the site of small airways, with these two manifestations mixed in various proportions in actual COPD cases (1). Dynamic hyperinflation, which refers to temporary increases in operating lung volumes above the resting value by air-trapping, has been shown to be more closely associated with dyspnea and intolerance during exercise than with FEV_1 and FEV_1/FVC (2). In addition, expiratory flow limitation during tidal breathing has been considered as a major determinant of dynamic hyperinflation and exercise limitation in COPD (3). Conversely, asthma shows reversible airflow limitations due to the constriction of airway smooth muscle, edema of the airway walls, mucous hypersecretion and increased airway inflammation (4). Some asthmatic patients, however, continue to show evidence of irreversible airflow limitation, even after aggressive treatment and the resolution of asth-

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matic symptoms, due to airway remodeling (5-7). The distribution of airway narrowing and the physiological mechanisms of airflow limitation may thus differ among asthma and COPD patients. However, spirometry cannot always distinguish the pathological and physiological mechanisms of airflow limitation due to asthma or COPD.

The impulse oscillation system (IOS) has been introduced into clinical practice recently. The IOS is a type of forced oscillation technique (FOT), which can evaluate respiratory resistance and reactance at various oscillatory frequencies to determine properties not assessable by spirometry (8, 9). The respiratory resistance (Rrs) component of respiratory impedance (Zrs) measured by IOS is a real part of Zrs while respiratory reactance (Xrs) is an theoretical part of Zrs. Theoretically, elastic properties of the lung are reflected in the low oscillatory frequencies of reactance, while inertial properties are dominantly reflected in the high oscillatory frequencies of reactance (10). In obstructive lung disease, further increases in Rrs and changes of Xrs to more negative at a lower oscillatory frequency have been reported (11). Also, it has been reported that there is a further change of Xrs to more negative in expiration of tidal breath measured by the FOT in COPD, and the within-breath changes in Xrs5 (ΔXrs5; the difference between expiratory and inspiratory reactance) have been suggested to represent the overall distribution of expiratory flow limitation during tidal breathing (13-15). IOS, however, is different from the classical FOT because an impulse (a rectangular wave form) rather than a pseudorandom noise signal (a mixture of several sinusoidal wave forms) is applied by a loud speaker, and there are differences in data processing. A limited number of studies have been published on IOS accuracy compared to FOT, and it has been generally suggested that the two methods yield similar but not identical measures of Rrs and Xrs (9).

The parameters of IOS which can clearly offer the distinction among the obstructive lung diseases have not been reported (16). The purpose of this study was to examine different patterns of changes in Rrs and Xrs at lower and higher oscillatory frequencies during tidal breathing between age-matched asthma and stable COPD patients using IOS, and to clarify differences in physiological airway mechanics between these two obstructive lung diseases.

Patients and Methods

Subjects

Subjects comprised 95 patients with stable COPD, 52 never-smoker patients with asthma, and 29 healthy never-smoker volunteers over 60 years old (in order to adjust for age among the three groups). All subjects had provided informed consent prior to participation, and all were Japanese. All patients with COPD displayed smoking-related COPD without α_1-antitrypsin deficiency and had a smoking history of more than 30 pack-years (packs smoked per day × year). COPD was diagnosed based on a clinical history of exertional dyspnea and pulmonary function characterized by not fully reversible airflow obstruction. Not fully reversible airflow obstruction is defined as $FEV_1/FVC < 70\%$ after the inhalation of a β_2-agonist and treatment with bronchodilators in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (1). Patients with any history of asthma or asthmatic symptoms, such as coughing or wheezing at rest in a stable phase, as well as patients who had taken oral steroids or had suffered from respiratory tract infection or exacerbation during the preceding 3 months were excluded from the COPD group. Among 95 patients with stable COPD, 67 patients were treated with a long-acting anti-cholinergic agent (tiotropium), 11 with short-acting anti-cholinergic agents, 27 with long-acting β_2-agonists, 12 with inhaled corticosteroids, 17 with salmeterol/fluticasone compounds (SFC), 35 with oral theophylline. Asthma was defined as a clinical history of intermittent wheezing, cough, chest tightness or dyspnea, documented diurnal variation in airflow limitation and reversible airflow obstruction either spontaneously or with treatment using inhaled β_2-agonist or inhaled corticosteroid, and bronchial hyperresponsiveness to methacholine. A diagnosis of asthma was made according to the guidelines of Global Initiative for Asthma (GINA) (4). Any patients with complications involving other obvious respiratory disorders or severe cerebral-cardiovascular disturbance were excluded. Among 52 patients with asthma, 37 patients were treated with inhaled corticosteroids, 15 with SFC, 26 with anti-leukotriene receptor antagonists, 15 with long-acting β_2-agonists, 21 with oral theophylline. We invited public participation in this study as healthy volunteers. None of the volunteers displayed any past history or symptoms of respiratory disorder or allergic disease.

Protocol and Measurements

During the first visit, history of the current illness was obtained, including complications and histories of smoking and allergic diseases, and a physical examination, laboratory examinations, and chest radiography were performed. All patients were instructed to continue all of their usual medications, but to withhold short-acting β_2-agonists and anti-cholinergic agents for 12 hour, slow-release theophylline for 24 hour, and long-acting β_2-agonists and anti-cholinergic agents (tiotropium) for 48 hour before pulmonary function testing. At the second visit, after obtaining informed consent, pulmonary function tests and measurements of respiratory impedance were examined using the IOS. This study was approved by the institutional research ethics committee of Shinshu University School of Medicine, and informed consent was obtained from all patients and volunteers.

Pulmonary Function Test

Spirometry and measurements of DLco were performed using a pulmonary function testing system (Chestac-55V; Chest, Tokyo, Japan). FRC was measured using a Body Box (Medgraphic, Ann Arbor, MI), after which the subject im-

mediately inspired to TLC and expired maximally to RV, allowing calculation of lung volume and RV/TLC. Airway resistance (Raw) was also measured using the Body Box. Pulmonary function testing was performed in accordance with the findings of the ATS/ERS Task Force 2005 (17) by two specialized technicians. Tests were performed two or three times to guarantee repeatability. Concerning predicted values for FEV_1, VC and DLco Japanese local reference values (18) developed by the Japanese Respiratory Society were adopted, and predicted values for FRC and RV as measured by body plethysmography were determined using the formulae of Boren et al (19).

Measurement of Respiratory Impedance by IOS

Respiratory impedance was measured using the IOS (Masterscreen IOS; Erich Jaeger, Hoechberg, Germany), which was a commercially available oscillatory system fulfilling the standard recommendations (16, 20, 21). Brief rectangular electrical pulses containing a continuous power spectrum of 0-100 Hz were generated by a simple on/off control switch on a loudspeaker, at intervals of 0.2 s, and impulse duration was about 45 ms. The oscillating pressure signals were superimposed on the spontaneous breathing of the subject using the head generator technique. The head generator technique involves applying oscillating pressure signals around the head and at the mouth, considerably reducing the motion of the cheeks and minimizing the upper airway impedance shunt artifact (22). Measurements of respiratory impedance were performed during tidal breathing for 30 s in a sitting position. The subject supported their cheeks and mouth floor to reduce upper airway shunting while tests were performed. Pressure and airflow were recorded simultaneously at the subject's mouth. Frequency analysis was calculated using fast Fourier transformation. The ratio of pressure to resulting airflow constitutes the impedance of the respiratory system (Zrs), which is characterized by two components: Rrs and Xrs. Xrs undergoes a transition from negative to positive values with increasing frequency (*f*). The resonant frequency (*f*res) was determined as the frequency at which Xrs crossed zero and the elastic and inertial forces were equal in magnitude and opposite. Rrs and Xrs at lower oscillatory frequencies and Rrs at higher frequencies were evaluated at 5 Hz (Rrs5 and Xrs5) and 20 Hz (Rrs20) of oscillatory frequency. Measurements during inspiration and expiration were triggered by respiratory flow. We compared the mean values of Rrs5 and Xrs5 in separated inspiration and expiration of tidal breathing, and the difference between mean expiratory and inspiratory resistance (ΔRrs5) or reactance (ΔXrs5) among healthy never-smokers and patients with asthma or stable COPD. Each subject was examined more than three times and these values were averaged.

Data Analysis

The values shown in the text, figures and tables represent the means ± standard error of the mean (SEM). Data distributions of variables in the various groups were first assessed using Bartlett's test. When data for variables showed a normal distribution, comparisons were made using one-way analysis of variance, followed by multiple comparisons using the Tukey-Kramer method. When data for variables did not show a normal distribution, variables were compared using the Kruskal-Wallis test, followed by multiple comparisons among groups using the nonparametric Tukey-Kramer method. Comparisons of variables during inspiration and expiration phase were performed using paired *t*-tests. Simple ccorrelations between variables were examined by calculating Pearson's product correlation coefficient. All statistical analyses were performed using Windows-compatible software (Stat Flex ver. 5.0; Artech, Osaka, Japan). A value of $p<0.05$ was considered significant for the results of all statistical analyses.

Results

The characteristics of subjects in the three groups are shown in Table 1. The proportion of females and body mass index were significantly lower and height was significantly higher in the COPD group than in the control or asthma groups. Twenty-five patients with asthma showed FEV_1/FVC of <70% in spirometry under no treatment with bronchodilators, defined as having flow limitation (FL). The severity of COPD according to GOLD criteria (1) was graded as: stage 1 (mild) in 16 patients; stage 2 (moderate) in 39 patients; stage 3 (severe) in 28 patients; and stage 4 (very severe) in 12 patients.

The patients with both asthma and COPD showed significantly higher values of Zrs5, Rrs5 and Rrs5-Rrs20 and more negative values of Xrs5 when compared with the control group (Table 2). Furthermore, patients with asthma showed significantly higher values of Rrs20 than those in control and COPD groups. Significant increases in *f*res with more negative changes of Xrs5 were observed in both asthma and COPD groups, and *f*res and Rrs5-Rrs20 were further increased in the COPD group compared with those in the asthma group. Rrs5 and Xrs5 were significantly correlated with FEV_1 (r=-0.43 and r=0.43, respectively) and Raw (r=0.52 and r=-0.65, respectively) in COPD. However, the Rrs5 and Xrs5 in asthma were significantly correlated with Raw (r=0.56 and r=-0.47, respectively), but not with FEV_1 (r=-0.24 and r=0.23, respectively). We also compared the mean values of Rrs5 and Xrs5 in separated inspiration and expiration of tidal breathing. Mean values of Rrs5 in expiration were further increased from those in inspiration in all three groups. The within-breath changes in Rrs5 were significantly greater in asthma and COPD groups than in controls, but no significant difference was apparent between asthma and COPD groups (Fig. 1). Xrs5 did not show any significant changes between inspiration and expiration in control and asthma groups. However, in the COPD group the mean values of Xrs5 in expiration showed significant changes to more negative from those in inspiration.

Table 1. Characteristcs of Healthy Never Smokers (Control Group), Patients with Asthma (Asthma Group), and Patlents with Stable COPD (COPD Group)

Subjects	Control	Asthma	COPD
n	29	52	95
Male / female	12 / 17	24 / 28	88 / 7 **††
Age, years	69.8 ± 1.3	69.8 ± 0.8	71.4 ± 0.5
Body height, m	1.57 ± 0.01	1.57 ± 0.01	1.63 ± 0.01 **††
BMI, kg/m^2	23.3 ± 0.6	23.5 ± 0.5	21.5 ± 0.3 **††
Smoking, pack × years	0	0	61.4 ± 3.2 **††
VC, % of pred.	111.2 ± 3.5	99.6 ± 2.5 **	95.7 ± 2.3 **
FEV_1, L	2.38 ± 0.12	1.79 ± 0.08 **	1.46 ± 0.06 **††
FEV_1, % of pred.	104.9 ± 3.5	79.5 ± 2.9 **	55.3 ± 2.3 **††
FEV_1/FVC, %	79.3 ± 0.9	69.6 ± 1.2 **	51.1 ± 1.2 **††
FRC, % of pred.	116.1 ± 4.7	136.2 ± 7.1 *	130.8 ± 3.4 *
RV, % of pred.	108.1 ± 3.8	157.0 ± 7.7 **	200.8 ± 6.7 **††
RV/TLC, %	37.8 ± 1.1	47.1 ± 1.5 **	52.6 ± 1.1 **†
DLco, % of pred.	92.1 ± 2.8	82.1 ± 2.5 *	57.7 ± 2.3 **††
DLco/V_A, % of pred.	109.7 ± 4.1	104.4 ± 3.2	64.9 ± 2.9 **††
Raw, cmH_2O·s/L	1.53 ± 0.19	2.34 ± 0.26 *	3.62 ± 0.31 **††

Values represent mean ± SEM. BMI, body mass index; TLC, total lung capacity. *p<0.05 and **p<0.01 vs. Control group. †p<0.05 and ††p<0.01 vs Asthma group.

Table 2. Respiratory Impedance (Zrs5), Resistance (Rrs5) and Reactance (Xrs5) At 5Hz Resistance at 20 Hz (Rrs20) and Mean Rrs 5 and Xrs5 in Inspiration and Expiration among Healthy Never Smokers (Control Group n=29), Patients with Asthma (Asthma Group n=52), and Patients with Stable COPD (COPD Group n=95)

Subjects	Control	Asthma	COPD
Zrs5, kPa·s/L	0.32 ± 0.03	0.45 ± 0.02 **	0.47 ± 0.02 **
Rrs5, kPa·s/L	0.27 ± 0.02	0.41 ± 0.02 **	0.40 ± 0.02 **
Rrs20, kPa·s/L	0.25 ± 0.02	0.31 ± 0.01 **	0.25 ± 0.01 ††
Rrs5-Rrs20, kPa·s/L	0.02 ± 0.01	0.10 ± 0.01 **	0.15 ±0.01 **††
Xrs5, kPa·s/L	-0.10 ± 0.01	-0.18 ± 0.01 **	-0.22 ± 0.02 **
*f*res, Hz	15.7 ± 1.2	21.0 ± 1.0 **	25.5 ± 0.9 **††
Inspiratory Phase			
Rrs5, kPa·s/L	0.26 ± 0.02	0.35 ± 0.02 **	0.35 ± 0.02 **
Xrs5, kPa·s/L	-0.10 ± 0.01	-0.17 ± 0.01 **	-0.18 ± 0.01 **
Expiratory Phase			
Rrs5, kPa·s/L	0.31 ± 0.03 ‡	0.45 ± 0.02 **‡	0.45 ± 0.02 **‡
Xrs5, kPa·s/L	-0.09 ± 0.01	-0.18 ± 0.02 **	-0.26 ± 0.03 **†‡

Values represent mean ± SEM. *f*res, resonant frequency (frequency at which Xrs crosses zero). *p<0.05 and **p<0.01 vs. Control group. †p<0.05 and ††p<0.01 vs Asthma group. ‡p<0.01 vs. values during inspiration.

When the patients in the COPD group were classified into four subgroups of mild, moderate, severe and very severe according to GOLD guidelines (1), Rrs5 and Rrs5-Rrs20 were significantly increased and Xrs5 significantly changed to more negative values in moderate to very severe COPD, together with increases in *f*res in accordance with the severity of COPD, whereas no significant changes in Rrs20 were observed (Fig. 2). The mean values of Xrs5 in expiration showed significant changes to more negative values from those in inspiration in the severe and very severe COPD, and the ΔXrs5, difference in Xrs5 between inspiration and expiration, was also significantly marked in severe and very severe COPD patients than in control or mild to moderate COPD patients.

The patients with asthma were classified into two subgroups, and compared with controls. One group showed normal FEV_1/FVC (n=27) and the other showed FEV_1/FVC < 70% (n=25) under no treatment with bronchodilators. In both subgroups, Rrs5 and Rrs5-Rrs20 were higher and Xrs5 was more negative with increases in *f*res than those in controls (Fig. 3). These changes in asthmatics whose FEV_1/FVC was <70% had a tendency to be greater, but no significant differences were observed between the two subgroups. Also, FEV_1/FVC and FEV_1 in asthmatics with normal FEV_1/FVC

were significantly lower than those in controls (FEV_1/FVC; 76.6 ± 0.9% in asthmatics with normal FEV_1/FVC vs. 79.3 ± 0.9% in controls; FEV_1; 88.9 ± 3.8% in asthma with normal FEV_1/FVC vs. 111.2 ± 3.5% in controls). Significant within-breath changes in Xrs5 could not be found even in asthma whose FEV_1/FVC <70%, although mean ΔXrs5 (0.03 ± 0.02 kPa·s/L) was significantly greater than in controls (-0.02 ± 0.01 kPa·s/L) ($p<0.05$). There was no significant difference in Rrs5 between severe COPD (0.49 ± 0.03 kPa·s/L) and asthma whose FEV_1/FVC was <70% (0.43 ± 0.03 kPa·s/L) although the ΔXrs5 was significantly marked in severe COPD patients (0.17 ± 0.04 kPa·s/L). In COPD significant correlations were found between ΔXrs5 and FEV_1 (r=-0.42) and Rrs5 (r=0.69). However, there was a significant correlation between ΔXrs5 and Rrs5 (r=0.58, $p<0.01$), but not between ΔXrs5 and FEV_1 (r=-0.29, not significant) in asthma patients with FEV_1/FVC <70% (Fig. 4).

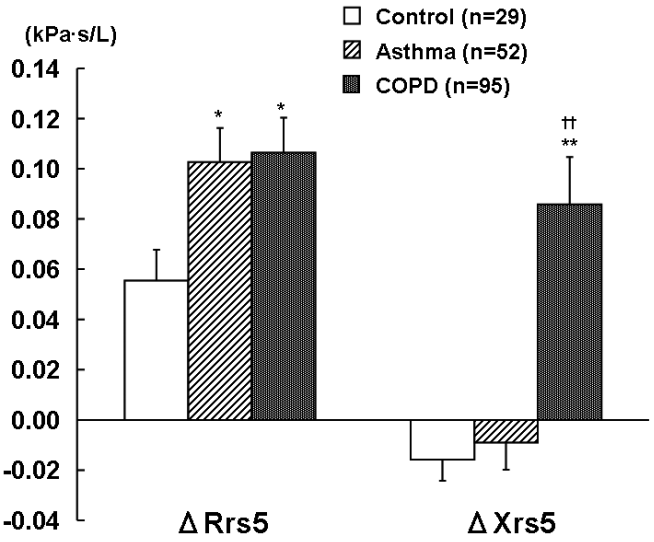

Figure 1. Comparison of within-breath changes in respiratory resistance at 5-Hz frequency (ΔRrs5) and respiratory reactance at 5-Hz frequency (ΔXrs5) among healthy never-smokers, asthma, and stable COPD groups.*p<0.05 and **p<0.01 vs. healthy never-smokers (Control group); ††p<0.01 vs. asthma group.

Discussion

In both asthma and COPD patients, a significant increase in Rrs5 and changes in Xrs5 to more negative and an associated increase in *f*res were observed. These pathological and physiological changes were remarkable in accordance with the severity of COPD, as previously reported (23, 24). In asthma, these changes in Rrs5 and Xrs5 were also observed in asthmatics with normal FEV_1/FVC (≧70%). Interestingly, the mean values of Xrs5 in expiration of tidal breathing significantly changed to a more negative value from that in inspiration in severe and very severe COPD patients, whereas no significant changes in Xrs5 between inspiration and expiration were observed in healthy never-smokers and asthma patients, even for asthma with FEV_1/FVC of <70% in spirometry. These findings suggest that IOS can detect changes in airway mechanics that cannot be found by spirometry alone in both asthma and COPD and that the large within-breath change in Xrs5, which may represent that airways easily collapse in expiration of tidal

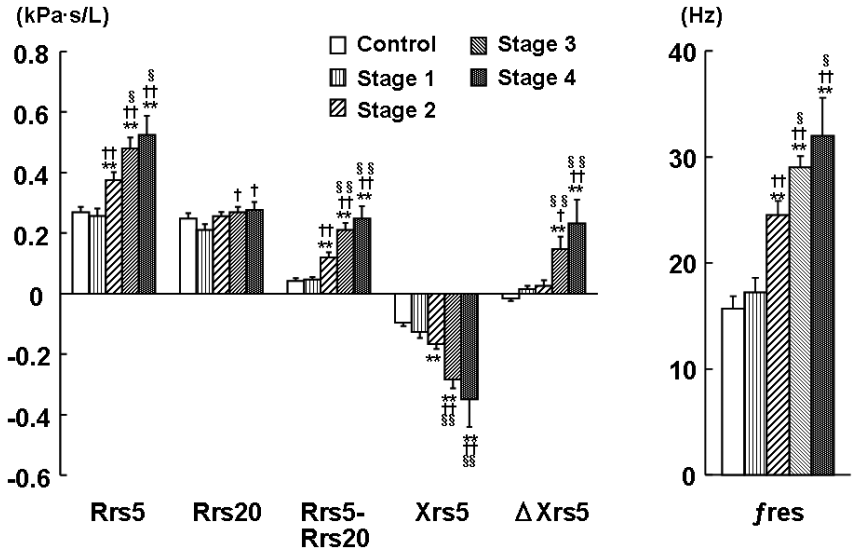

Figure 2. Respiratory resistance at 5-Hz frequency (Rrs5) and 20-Hz frequency (Rrs20), Rrs5-Rrs20, respiratory reactance at 5-Hz frequency (Xrs5), within-breath changes in Xrs5 (ΔXrs5) and resonant frequency (*f*res), which is the frequency at which Xrs crosses zero, as measured by an impulse oscillation system (IOS) in the four groups of COPD classified according to severity as determined by GOLD guidelines. *p<0.05 and **p<0.01 vs. healthy never-smokers (Control group); †p<0.05 and ††p<0.01 vs. stage 1 patients with COPD; §p<0.05 and §§p<0.01 vs. stage 2 patients with COPD.

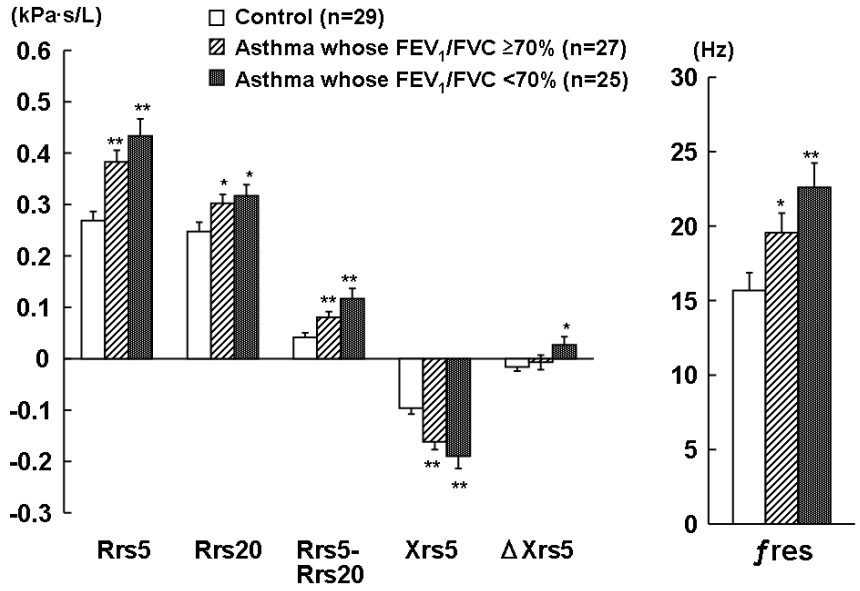

Figure 3. **Respiratory resistance at 5-Hz frequency (Rrs5) and 20-Hz frequency (Rrs20), Rrs5-Rrs20, respiratory reactance at 5-Hz frequency (Xrs5), within-breath changes in Xrs5 (ΔXrs5), and resonant frequency (*f*res), which is the frequency at which Xrs crosses zero, as measured by an impulse oscillation system (IOS) in asthmatics whose FEV_1/FVC is ≥70% and whose FEV_1/FVC is <70% (under no treatment with bronchodilators).*p<0.05 and **p<0.01 vs. healthy never-smokers (control group).**

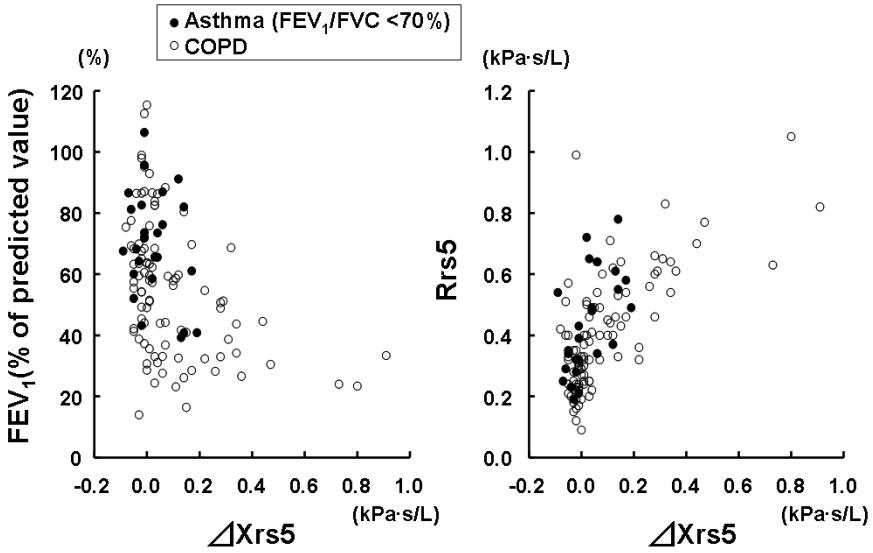

Figure 4. **Relationship between the within-breath change in respiratory reactance at 5 Hz (ΔXrs5) of oscillatory frequency and FEV_1 (left side panel) or respiratory resistance at 5 Hz oscillatory frequency (Rrs5) (right side panel) in asthmatics whose FEV_1/FVC is <70% (n=25) and in COPD patients (n=95).**

breath, may be an interesting finding in severe and very severe COPD patients.

Predictive equations for Rrs5, Rrs20 and Xrs5 in normal Japanese adults have been established by Shiota et al (25) and are dependent on the log of height for Rrs5 and Rrs20 and on age and log of height for Xrs5, independent of sex. Adoption of the predictive equations in the present study yielded similar results except for Rrs20. However, these predictive equations were not adopted in this study, as mean age was much lower in the reference population than in the study groups.

The increases in Rrs5 and the changes of Xrs5 to more negative were also observed in asthma with normal FEV_1/FVC, and the mean values of Rrs5 and negative values of Xrs5 were significantly correlated with Raw, but not with FEV_1. These discrepancies were not observed in COPD patients. The diagnostic sensitivity for asthma is reported to be better using IOS (31.3%) than conventional pulmonary func-

tion tests (19.6%), whereas spirometry offers better sensitivity (47.4%) than IOS (39.0%) among cases of COPD, and the specificity was comparable for IOS and spirometry in relation to asthma and COPD (26). In patients with mild asthma, FEV_1 may also be close to normal and is not as sensitive as IOS for measuring small changes in lung function in response to bronchodilators and asthma therapy (27, 28). It has also been demonstrated that the increases in Rrs and changes of Xrs to more negative at lower oscillatory frequencies in the response to experimentally induced changes in airway obstruction proceed the fall in FEV_1 (11, 29). In the present study, to evaluate the sensitivity and specificity of spirometry and IOS to differentiate asthma from control subjects, we performed receiver operating characteristic (ROC) analysis for FEV_1/FVC and Rrs5. The area under the curve (AUC) in ROC analysis was 0.82 for FEV_1/FVC and 0.79 for Rrs5. However, when the cut-off level of FEV_1/FVC was 70%, the sensitivity and specificity were 48.1% and 100%, respectively. When the cut-off level of Rrs5 was 0.32 kPa·s/L, the sensitivity and specificity were 69.3% and 72.4%, respectively. Rrs5 is more sensitive than FEV_1/FVC of <70%. Several mechanisms may account for these differences, including the need for deep inspiration prior to spirometry which may alter bronchial tone in asthma (30). IOS may be more sensitive than spirometry for detecting abnormalities in the airway mechanics of asthma patients. A significant increase in Rrs20 was only observed in asthma, however, the resistance particularly at higher oscillatory frequencies may be largely affected by upper airway shunt, and the Rrs20 cannot be evaluated precisely. So, the pattern of changes in Rrs and Xrs5 could not distinguish COPD from asthma.

As one limitation, the lung volume, which affects measurements of resistance, can not be measured by IOS. Rrs has been shown to display a significant negative correlation with RV/TLC in healthy subjects, but shows a positive correlation with RV/TLC in COPD patients (31). In the present study, significantly positive correlations between Rrs5 and RV/TLC in asthma (r=0.49) and COPD (r=0.46) were observed. This phenomenon may be attributable to lung hyperinflation resulting from air-trapping in both asthma and COPD. Conversely, Xrs5 is likely to be insensitive to volume-dependent effects, and sensitive to complete and partial expiratory flow limitations (13, 15). The other limitation was that the machine could display the time-course polygraph of volume and flow and pressure, but not display the time-course polygraph of real changes of Rrs and Xrs within tidal breathing. If the real changes of these parameters during tidal breathing can be displayed, the pattern of the large within-breath changes of Xrs5 observed in severe COPD can be evaluated visually and our assertion will be supported strongly.

The chronic airflow limitation characteristic of COPD is well known to be caused by a combination of both small airway disease and parenchymal destruction (1). These changes diminish the ability of the airways to remain open during expiration. As a consequence, the airways become partly collapsed and the lumen becomes occluded even during tidal breathing in cases of severe COPD (2, 3). The most interesting observation in the present study was the further change of Xrs5 to more negative in expiration during tidal breathing in severe and very severe COPD patients, whereas no significant within-breath changes in Xrs5 were observed in healthy never-smokers and asthma patients, even in asthma with FEV_1/FVC of <70%. Peslin et al (32, 33) reported that some COPD patients developed large negative swings in respiratory system reactance during mechanical ventilation, and Dellaca et al (13-15) indicated that respiratory system reactance measured by FOT changed to be more negative values during flow-limited expiration in patients with COPD. When airflow limitation is present, the oscillatory signal cannot pass through the choke points to reach the alveoli (12), resulting in a marked reduction in apparent compliance and thus the value of Xrs5 changes to be more negative physiologically (34). The within-breath changes in Xrs5 have been suggested to reflect the number of choke points present and the distribution within the bronchial tree, and to represent the overall distribution of expiratory flow limitation during tidal breathing (13-15). In COPD, as airflow obstruction worsens, expiratory flow limitation appears at much lower flows for a given lung volume and becomes present at rest or at least early during exercise (35). In the present study, a significant increase in Rrs5 in expiration from that in inspiration was observed in all three groups, and there was no difference in the within-breath changes in Rrs5 between asthma and COPD patients. However, a significant change in Xrs5 between inspiration and expiration was not found even in asthmatics with FEV_1/FVC of <70%, and no significant difference in ΔXrs5 between asthmatics with FEV_1/FVC of ≥70% and those with FEV_1/FVC of < 70%, whereas the large within-breath changes in Xrs5 was apparently observed in a large number of severe COPD patients. Also, a significant correlation was found between ΔXrs5 and FEV_1 in COPD, but in asthma with obstructive lung function, there was no significant correlation between ΔXrs5 and FEV_1. It is very difficult to understand the discrepancy between the within-breath changes of Rrs5 and Xrs5 in asthma and severe COPD. Furthermore, we could not conclude whether the larger within-breath changes in Xrs5 is a specific phenomenon in severe COPD or not, because the severity of airflow obstruction expressed as FEV_1 in asthma was milder when compared with that in COPD. The forced expiration maneuver emphasizes the airway collapsibility by the increase in intra-thoracic pressure. Even though there was no difference in respiratory resistance at rest between asthma and COPD, the COPD patients showed more severe airflow obstruction by the airway collapsibility when the patient did forced expiration. It may be difficult to explain the mechanism of large within-breath changes in Xrs5 during tidal breathing in severe COPD, which may represent the presence of air-trapping due to easy collapsibility of small airways in expiration during tidal breathing.

In conclusion, IOS may be useful for detecting pathophysiological changes of the respiratory system in accordance with the severity of COPD and even at an earlier stage of asthma with normal spirometry, and the larger within-breath change of Xrs5 during tidal breathing in severe COPD may represent easy collapsibility of the small airways. These properties may help to analyze airway mechanics and to identify abnormalities of the airways that can not be found by spirometry alone.

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