Characteristics of inspiratory and expiratory reactance in interstitial lung disease

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Summary
Background: Forced oscillometry is a non-invasive method to measure respiratory resistance and reactance. In this study, we investigated the characteristics of measurements obtained with an impulse oscillation system (IOS) for patients with interstitial lung disease (ILD).
Method: IOS and spirometry were performed in 64 ILD patients, 54 asthma patients, 49 chronic obstructive pulmonary disease (COPD) patients, and 29 controls. Respiratory resistance and reactance were assessed as measurements averaged over several tidal breaths (whole-breath analysis) and as measurements separately averaged during inspiration and expiration (inspiratory–expiratory analysis).
Results: Whole-breath IOS analyses for ILD patients showed increased resistance at 5 Hz and decreased reactance at 5 Hz (X5) compared with controls, although these features were also found in asthma and COPD patients. Inspiratory–expiratory analysis demonstrated that the changes in X5 and reactance area (AX) between inspiration and expiration (ΔX5 and ΔAX, respectively) were significantly different from those in asthma patients, COPD patients, and controls. However, multiple linear regression analysis showed that the presence of ILD was independently associated with ΔX5, but not with ΔAX. Furthermore, ΔX5 was inversely correlated with vital capacity and diffusing capacity of carbon monoxide in ILD patients.
Conclusions: Our results suggest that ΔX5 is a characteristic feature of IOS measurements in ILD patients, which is clearly different from those in asthma and COPD patients. This within-breath X5 change in ILD might be associated with its severity and physiological abnormality, although further studies are needed to investigate its cause.
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Introduction

Interstitial lung disease (ILD) is a group of lung diseases with diverse clinical and histopathological manifestations that share a common physiological abnormality of restrictive ventilation.[1] In patients with ILD, a static expiratory pressure—volume curve of the lung is generally shifted downward and rightward and spirometry results reveal reduced vital capacity.[2] However, reduced vital capacity may occur even in patients with obstructive lung diseases and in other situations, such as chest wall restriction, lung resection, inspiratory muscle weakness, or poor cooperation with spirometry. In addition, spirometry is sometimes difficult to perform with elderly, cognitively impaired patients, or patients with severe respiratory distress.[3]

Forced oscillometry is a non-invasive method to measure respiratory impedance and generally requires only passive patient cooperation. Two components of respiratory impedance can be evaluated by forced oscillometry: total respiratory resistance and reactance.[4] Resistance at low frequency, 5 Hz (R5), indicates total airway resistance and resistance at high frequency, 20 Hz (R20), approximates central airway resistance. The difference between R5 and R20 (R5 − R20) is considered to be an index of the small airways.[3] Reactance at 5 Hz (X5) is thought to be reciprocally related to compliance. The resonant frequency (Fres) is the intermediate frequency at which the total reactance is 0, and reactance area (AX) is the integrated low frequency respiratory reactance magnitude (area under the curve) between 5 Hz to Fres.[5] X5, Fres, and AX have been proposed for detecting expiratory flow limitations.[6-8]

Forced oscillometry has been used primarily for patients with obstructive lung diseases because it can sensitively detect increased airway resistance.[4] Additionally, Dellaca et al. reported that reactance assessed separately during inspiration and expiration (inspiratory—expiratory analysis) using forced oscillometry can accurately detect expiratory flow limitation.[6] Inspiratory—expiratory analysis is useful to differentiate chronic obstructive pulmonary disease (COPD) patients from asthmatics who have the same degree of airflow limitation evaluated by spirometry.[7] However, characteristic findings of forced oscillometry performed for patients with restrictive lung diseases such as ILD have not been fully demonstrated[9-13] and, to the best of our knowledge, there has been no published data regarding inspiratory—expiratory analysis using forced oscillometry in patients with ILD. To date, forced oscillometry has not been shown to be able to distinguish between restrictive and obstructive lung disease.[9,10]

In the present study, in order to investigate the characteristics of data obtained by forced oscillometry performed for patients with ILD, we measured respiratory resistance and reactance at both inspiratory and expiratory phases using an impulse oscillation system (IOS) in control subjects and in patients with ILD, COPD, and asthma. We also evaluated the relationships between the IOS measurements and results from pulmonary function tests for patients with ILD.

Materials and methods

Subjects

This was a retrospective observational study for subjects who had spirometry tests and IOS measurements at the Hiroshima University Hospital (Hiroshima, Japan) between December 2007 and April 2011. We enrolled 64 patients with ILD (36 males; mean age 65.8 ± 0.9 years), 54 patients with asthma (13 males; mean age 52.1 ± 2.6 years), 49 patients with COPD (40 males; mean age 71.5 ± 1.4 years), and 29 control subjects (19 males; mean age 47.6 ± 2.5 years). All ILD patients were diagnosed in accordance with the clinical criteria established by the current ATS/ERS guidelines.[1] Patients with ILD whose forced expiratory volume in 1 s (FEV$_1$)/forced vital capacity (FVC) ratio was <70% and/or who had a history of asthma were excluded from this study. Three ILD patients whose FEV$_1$/FVC ratios were <70% were excluded. All 3 of these patients were heavy smokers with rheumatoid arthritis and their CT results demonstrated the presence of apparent emphysema.

Clinical or histopathological diagnoses in the 64 enrolled patients with ILD were: idiopathic pulmonary fibrosis (IPF) in 26, nonspecific interstitial pneumonia (NSIP) in 17, chronic hypersensitivity pneumonia (CHP) in 7, collagen-vascular disease associated interstitial pneumonia (CVD-IP) in 13, and desquamative interstitial pneumonia in one patient. Regarding CVD-IP, cases whose chest CT results showed a usual interstitial pneumonia (UIP) or NSIP pattern were selected. Ten patients were treated with corticosteroids alone, two patients were treated with corticosteroids plus immunosuppressive agents, and one patient was treated with an immunosuppressive agent alone. Asthma diagnosis was made based on clinical history plus historical evidence of reversible airway obstruction. To avoid the possible complication of COPD, only asthmatic patients who never smoked were enrolled. For the 54 enrolled patients, asthma severity based on the Global Initiative for Asthma (GINA) criteria[14] was step 1 for 7 patients (13.0%), step 2 for 11 patients (20.4%), step 3 for 12 patients (22.2%), step 4 for 18 patients (33.3%), and step 5 for 6 patients (11.1%). All enrolled asthma patients had not suffered from exacerbations during the previous month. Among the 54 patients with asthma, inhaled corticosteroids were used by 44 patients, long acting β_2-agonists were used by 22 patients, anti-leukotriene receptor antagonists were used by 14 patients, and oral theophylline was used by 11 patients. A COPD diagnosis was based on the Global Initiative for Obstructive Lung Disease (GOLD) criteria.[15] COPD severity according to the GOLD criteria was stage 1 (mild) for 6 patients, stage 2 (moderate) for 24, stage 3 (severe) for 18, and stage 4 (very severe) for 1. Each enrolled COPD patient was clinically stable. Among the 49 COPD patients, a long acting anti-cholinergic agent was used by 20 patients, long acting β_2-agonists were used by 19 patients, and inhaled corticosteroids were used by 13 patients. All of the control subjects were non-current smokers who had visited the Hiroshima University Hospital for medical health check-ups. Spirometric results for all control subjects were FEV$_1$/FVC ratio >70% and vital capacity (VC) >80% of predicted. None of the control subjects had evidence of pulmonary

disease based on their histories and physical examination results.

All subjects were informed of the possibility of being enrolled in a retrospective observational study when they had spirometry tests and IOS measurements, and all provided permission to use their de-identified data. The institutional review board approved this retrospective observational study and waived the requirement to obtain informed consent.

Forced oscillometry

In this study, we used IOS (Eric Jaeger, Germany) to assess respiratory impedance. IOS measurements were performed before spirometry. Impulses were applied for 30 s during tidal breathing in a sitting position. Subjects supported their cheeks with both hands to reduce upper airway shunting and wore nose clips to avoid air leaks. R5, R20, R5 − R20, X5, Fres, and AX were evaluated. We compared the data for R5, R20, R5 − R20, X5, Fres, and AX measured at inspiratory and expiratory phases. The results for each of these variables were determined using IOS software by separately averaging the measurements obtained during inspiration and expiration. Within-breath changes in X5 (ΔX5), defined as expiratory X5 minus inspiratory X5, and in AX (ΔAX), defined as expiratory AX minus inspiratory AX, were compared among the four groups.

Pulmonary function tests

Spirometry and diffusion capacity for carbon monoxide (DLco) measurements were made by one specialist technician, as previously recommended.[16] Predicted values for FEV_1, VC, and DLco were determined based on reference values.[17,18] DLco was determined only for the patients with ILD using a single-breath technique. All DLco measurements were corrected to the standard haemoglobin value according to ERS/ATS standards.[19]

Statistical analysis

Results are expressed as the means ± standard errors of the means (SEMs). A value of $p < 0.05$ was considered to indicate a significant difference. The Mann−Whitney test was applied to examine differences between groups. Multiple linear regression analysis was used to assess the relative contributions of age, sex, height, weight, body mass index (BMI), and smoking status (pack-years) on ΔX5 and ΔAX in the study groups (control, asthma, COPD, and ILD). Pearson correlation analysis was used to assess associations between ΔX5 and %VC or %DLco in ILD patients. A Kruskal−Wallis test was used to compare the results for each variable among ILD subgroups. Statistical analyses were performed using the JMP software suite (SAS Institute).

Results

The subjects enrolled in the study were classified into control, asthma, COPD, and ILD groups. The subjects' characteristics are summarized in Table 1. Subjects in the COPD group were the oldest and had the highest pack-year smoking history among the four groups. The ILD group showed the lowest VC and the COPD group had the lowest FEV_1. The characteristics of the ILD subgroups (IPF, NSIP, CHP, and CVD-IP) are also summarized in Supplemental Table 1.

The whole-breath IOS results for the four groups are shown in Table 2. The whole-breath IOS results for ILD subgroups are also shown in Supplemental Table 2. R5 values in the control group (0.26 ± 0.01 kPa/L/s) were significantly lower than those in the asthma group (0.38 ± 0.02 kPa/L/s; $p < 0.0001$), the COPD group (0.42 ± 0.03 kPa/L/s; $p < 0.0001$), and the ILD group (0.31 ± 0.01 kPa/L/s; $p < 0.05$). However, R5 in the asthma or the COPD group was shown to be significantly higher as compared with that in the ILD group. While R20 was significantly higher in the asthma group than in the control group, there was no difference in R20 between the patients with ILD and the control subjects. R5 − R20 values were the highest in the COPD group among the four groups and were significantly higher in the asthma or the ILD group than in the control subjects.

Regarding X5, as compared with the control subjects (−0.10 ± 0.01 kPa/L/s), X5 values were significantly more negative in the patients with asthma (−0.16 ± 0.01 kPa/L/s; $p < 0.01$), COPD (−0.20 ± 0.02 kPa/L/s; $p < 0.0001$), and ILD (−0.16 ± 0.01 kPa/L/s; $p < 0.0001$). Fres and AX values in the asthma, COPD, and ILD groups were significantly higher than

Table 1 Study subjects' characteristics.

	Control ($n = 29$)	Asthma ($n = 54$)	COPD ($n = 49$)	ILD ($n = 64$)
Male/Female	19/10	13/41*	40/9†	36/28†#
Age (years)	47.6 ± 2.5	52.1 ± 2.6	71.5 ± 1.4*†	65.8 ± 0.9*†#
Body height (m)	1.65 ± 0.02	1.55 ± 0.01*	1.61 ± 0.01*†	1.58 ± 0.01*†
BMI (kg/m^2)	23.3 ± 0.4	23.0 ± 0.6	21.8 ± 0.4*	23.1 ± 0.5
Smoking history Current/Ex/Never	0/10/19	0/0/54	9/38/2	6/35/23
Pack-years	3.0 ± 1.1	0*	53.9 ± 3.8*†	27.5 ± 3.5*†#
VC (% predicted)	105.1 ± 1.8	95.1 ± 2.6*	87.6 ± 2.9*†	76.1 ± 2.6*†#
FEV_1 (% predicted)	103.2 ± 2.1	86.1 ± 2.8*	58.5 ± 2.6*†	79.6 ± 2.4*#

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; VC = vital capacity; FEV_1 = forced expiratory volume in 1 s. Results are means ± SEMs. p-Values are not significant unless indicated. *$p < 0.05$: vs. control group. †$p < 0.05$: vs. asthma group. #$p < 0.05$: vs. COPD group.

Table 2 Whole-breath IOS results.

	Control (n = 29)	Asthma (n = 54)	COPD (n = 49)	ILD (n = 64)
R5 (kPa/l/s)	0.26 ± 0.01	0.38 ± 0.02*	0.42 ± 0.03*	0.31 ± 0.01*†#
R20 (kPa/l/s)	0.24 ± 0.01	0.32 ± 0.01*	0.28 ± 0.01†	0.24 ± 0.01†
R5 − R20 (kPa/l/s)	0.02 ± 0.01	0.07 ± 0.01*	0.13 ± 0.02*†	0.07 ± 0.01*#
X5 (Pa/l/s)	−0.10 ± 0.01	−0.16 ± 0.01*	−0.20 ± 0.02*	−0.16 ± 0.01*
Fres (Hz)	10.57 ± 0.57	14.82 ± 0.71*	20.76 ± 0.98*†	15.74 ± 0.51*#
AX (kPa/l/s Hz)	0.28 ± 0.02	0.79 ± 0.13*	1.56 ± 0.22*†	0.77 ± 0.01*#

COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; R5 = resistance at 5 Hz; R20 = resistance at 20 Hz; X5 = reactance at 5 Hz; Fres = resonant frequency; AX = reactance area. Results are means ± SEMs. p-values are not significant unless indicated. *$p < 0.05$: vs. control group. †$p < 0.05$: vs. asthma group. #$p < 0.05$: vs. COPD group.

those for the control subjects. Next, we separately calculated the average values for R5, R20, R5 − R20, X5, Fres, and AX during expiration and inspiration; these within-breath IOS measurements are shown in Table 3. The within-breath IOS results for subgroups of ILD (IPF, NSIP, CHP, and CVD-IP) are also shown in Supplemental Table 3. As shown in Fig. 1A, expiratory R5 was significantly higher than inspiratory R5 in all groups. Similarly, expiratory R20 was higher than inspiratory R20 in all groups but a statistically significant difference was not observed in the patients with COPD (Fig. 1B).

Interestingly, expiratory R5 − R20 was significantly higher than inspiratory R5 − R20 in the COPD group, whereas there were no significant differences in R5 − R20 between expiration and inspiration in the asthma group, the ILD group, and the control subjects. In contrast to the changes in R5 and R20 between expiration and inspiration, the changes in X5 between inspiration and expiration were found to vary among the four groups (Fig. 1C). In the

control subjects and the patients with asthma, there was no significant difference between expiratory X5 and inspiratory X5. In the patients with COPD, expiratory X5 (−0.23 ± 0.03 kPa/L/s) was more negative than inspiratory X5 (−0.16 ± 0.01 kPa/L/s) ($p < 0.05$). In the patients with ILD, however, expiratory X5 (−0.14 ± 0.013 kPa/L/s) was found to be significantly less negative than inspiratory X5 (−0.19 ± 0.01 kPa/L/s) ($p < 0.0001$).

In the ILD group, there was a trend for increased inspiratory AX (0.86 ± 0.08 kPa/L/s) compared to expiratory AX (0.74 ± 0.07 kPa/L/s), whereas Fres did not differ between inspiration (15.54 ± 0.47 kPa/L/s) and expiration (15.89 ± 0.57 kPa/L/s) (Table 3). Supporting the changes seen in X5 between expiration and inspiration among the four groups, ΔX5 in the ILD group (0.04 ± 0.01 kPa/L/s) was significantly higher than those in the other three groups, and ΔX5 in the COPD group (−0.08 ± 0.02 kPa/L/s) was significantly lower than those in the other three groups

Table 3 Inspiratory−expiratory IOS results.

	Control (n = 29)	Asthma (n = 54)	COPD (n = 49)	ILD (n = 64)
R5 (kPa/l/s)				
Expiratory	0.28 ± 0.02§	0.41 ± 0.02*§	0.45 ± 0.03*§	0.32 ± 0.01†#§
Inspiratory	0.23 ± 0.01	0.34 ± 0.02*	0.37 ± 0.02*	0.29 ± 0.01*†#
R20 (kPa/l/s)				
Expiratory	0.26 ± 0.02§	0.33 ± 0.01*§	0.30 ± 0.01†	0.25 ± 0.01†#§
Inspiratory	0.22 ± 0.01	0.29 ± 0.01*	0.26 ± 0.01*†	0.22 ± 0.01†#
R5 − R20 (kPa/l/s)				
Expiratory	0.02 ± 0.01	0.08 ± 0.01*	0.16 ± 0.02*†§	0.07 ± 0.01*#
Inspiratory	0.01 ± 0.01	0.05 ± 0.01*	0.10 ± 0.01*†	0.07 ± 0.01*#
X5 (kPa/l/s)				
Expiratory	−0.10 ± 0.01	−0.16 ± 0.02*	−0.23 ± 0.03*†§	−0.14 ± 0.01*#§
Inspiratory	−0.11 ± 0.01	−0.16 ± 0.01*	−0.16 ± 0.01*	−0.19 ± 0.01*†#
ΔX5	0.02 ± 0.01	0.00 ± 0.01	−0.08 ± 0.02*†	0.04 ± 0.01*†#
Fres (Hz)				
Expiratory	10.70 ± 0.67	15.30 ± 0.82*	21.75 ± 1.02*†§	15.89 ± 0.57*#
Inspiratory	10.46 ± 0.49	13.80 ± 0.62*	19.04 ± 0.96*†	15.54 ± 0.47*†#
AX (kPa/l/s Hz)				
Expiratory	0.26 ± 0.05	0.88 ± 0.15*	1.87 ± 0.24*†§	0.74 ± 0.07*#
Inspiratory	0.28 ± 0.05	0.67 ± 0.10*	1.04 ± 0.12*†	0.86 ± 0.08*†
ΔAX	−0.02 ± 0.03	0.22 ± 0.08*	0.82 ± 0.18*†	−0.12 ± 0.06*†#

COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; R5 = resistance at 5 Hz; R20 = resistance at 20 Hz; X5 = reactance at 5 Hz; Fres = resonant frequency; AX = reactance area. Results are means ± SEMs. p-values are not significant unless indicated. *$p < 0.05$: vs. control group. †$p < 0.05$: vs. asthma group. #$p < 0.05$: vs. COPD group. §$p < 0.05$: vs. inspiratory phase.
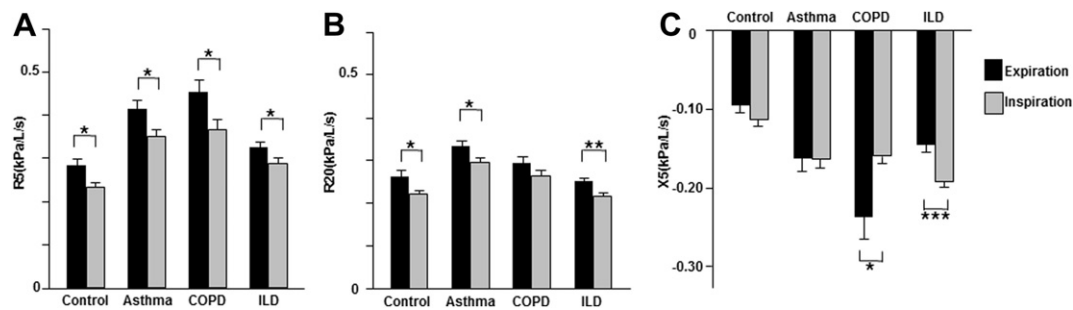
Figure 1 Comparisons of the mean values for resistance at 5 Hz (R5) (A), resistance at 20 Hz (R20) (B) and reactance at 5 Hz (X5) (C) during expiration and inspiration in the control ($n = 29$), asthma ($n = 54$), chronic obstructive pulmonary disease (COPD) ($n = 49$), and interstitial lung disease (ILD) ($n = 64$) groups. Error bars indicate standard errors of the mean. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.0001$.

(Fig. 2A). In addition, ΔAX values in the ILD group were significantly different from those in the other three groups (Fig. 2B). Among the asthma, COPD, ILD, and control groups, the variables of age, sex, height, weight, BMI, and smoking status (pack-years) were not completely matched; these differences might have affected the ΔX5 and ΔAX values. Therefore, we used multiple linear regression analysis to determine what variables were significantly associated with ΔX5 or ΔAX levels.

This analysis showed that ΔX5 was independently associated with the presence of COPD ($\beta = -0.428$; $p < 0.0001$) or ILD ($\beta = 0.192$; $p = 0.037$), but was not associated with age, sex, height, weight, BMI, or smoking status (pack-year) (Table 4). The only significant variable associated with ΔAX was the presence of COPD. An independent association between the presence of ILD and ΔAX was not found. This result implied that ΔX5 was a more characteristic feature of IOS measurements in ILD patients than was ΔAX (Table 4). Based on these results, relationships between ΔX5 and measurements of pulmonary function tests (%VC and % DLco) were analysed for ILD patients (Fig. 3). ΔX5 was inversely correlated with %VC ($r = -0.43$; $p < 0.001$) and % DLco ($r = -0.57$; $p < 0.0001$).

Discussion

In the present study, the characteristics of IOS measurements made for patients with ILD were described in detail. To the best of our knowledge, this is the first report to compare IOS data between patients with restrictive and obstructive lung diseases. Whole-breath IOS analyses for ILD patients showed increased R5 and decreased X5 compared with controls, although these features were also found in the asthma and COPD groups. However, changes in IOS measurement results, particularly X5 and AX, between inspiration and expiration were characteristic features in asthma, COPD, and ILD. Inspiratory and expiratory X5 did not differ in the control subjects and the patients with asthma. The magnitudes of expiratory X5 were greater than those of inspiratory X5 in the patients with COPD, while this situation was found to be reversed in the patients with ILD. Similarly, the within-breath changes in AX were significantly lower in ILD patients than those in asthma or COPD patients; however, multiple linear regression analysis showed that the presence of ILD was not independently associated with ΔAX. These results indicate that patients with ILD show completely different characteristics of
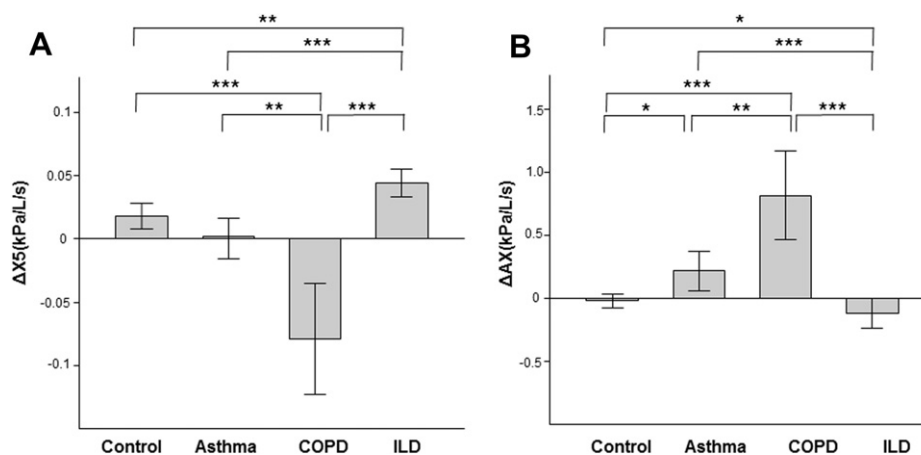

Figure 2 Comparison of the mean values for ΔX5 (expiratory–inspiratory values of the reactance at 5 Hz) (A) and ΔAX (expiratory–inspiratory values of the reactance area) (B) in the control group ($n = 29$), patients with asthma ($n = 54$), patients with chronic obstructive pulmonary disease (COPD) ($n = 49$), and patients with interstitial lung disease (ILD) ($n = 64$). Error bars indicate standard errors of the mean. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.0001$.

Table 4 Multiple linear regression analysis for ΔX5 and ΔAX.

Variables	ΔX5		ΔAX	
	Standardized coefficient (β)	p-Value	Standardized coefficient (β)	p-Value
Age	−0.006	0.946	−0.046	0.601
Sex	−0.055	0.548	0.045	0.634
Height	0.186	0.656	0.247	0.565
Weight	−0.267	0.687	−0.456	0.503
BMI	0.027	0.958	0.607	0.244
Smoking (pack-years)	0.074	0.417	−0.082	0.382
Control	0.072	0.350	−0.119	0.131
COPD	−0.428	<0.0001	0.449	<0.0001
ILD	0.192	0.037	−0.047	0.616

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease. Sex: female = 0, male = 1; Control: no = 0, yes = 1; COPD: no = 0, yes = 1; ILD: no = 0, yes = 1. The presence of asthma was excluded from this multiple linear regression model.

within-breath changes in X5 as compared with asthma and COPD patients. In addition, a significant correlation between ΔX5 and %VC or %DLco suggests that the within-breath change in X5 may be associated with a physiological abnormality in ILD.

The most interesting finding of this study was that the within-breath change in X5 was a distinguishable characteristic of ILD as compared with the change in asthma or COPD. As previously reported, there was no difference in X5 by whole-breath oscillometry between ILD and asthma or COPD.[9,10] The magnitude of inspiratory X5 was shown to be greater than that of expiratory X5 in the patients with ILD. Consistent with the results of previous studies,[3,6–8] the inspiratory and expiratory X5 did not differ in the asthma patients and the magnitude of inspiratory X5 was smaller than that of expiratory X5 in the patients with COPD. X5 is a numerically negative value thought to be related to the reciprocal of lung compliance.[5,20] Therefore, its value becomes more negative when the peripheral lung tissue has reduced compliance or is compressed.[20,21] Because the distensibility of peripheral lung tissue is decreased in patients with ILD,[2] compliance during inspiration is likely to be more reduced compared with that during expiration. This might be a reason why the magnitude of inspiratory X5

was greater than that of expiratory X5 in patients with ILD. Furthermore, the different patterns of within-breath changes in X5 among the patients with asthma, COPD, and ILD suggest that inspiratory–expiratory analysis using IOS might be useful not only for obstructive lung disease but also for ILD. Further investigations will be needed to identify the cause(s) of these differences of within-breath changes in X5.

Another interesting finding of this study was that ΔX5 showed significant inverse correlations with VC and DLco in patients with ILD. Because reduced lung volume and diffusion capacity are associated with ILD disease severity and prognosis,[22,23] our results may support the association between ΔX5 and disease severity or physiological abnormality in ILD. The inverse correlation between ΔX5 and VC may also suggest an association between increased ΔX5 and reduced lung distensibility in ILD. In addition, the greater magnitude of ΔX5 resulting from exaggerated inspiratory reactance may reflect an increased elastic recoil during inspiration in ILD.

For patients with ILD, whole-breath analyses of IOS demonstrated that R5 and R5 − R20 were increased, but that R20 was similar compared with those of the control subjects. Resistance represents the frictional components of the respiratory tract and is predominantly influenced by
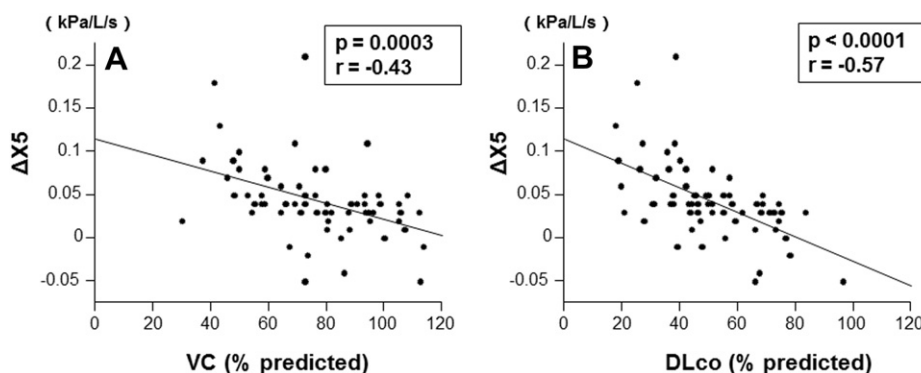

Figure 3 Relationship between ΔX5 and VC% predicted (A) or DLco% predicted (B) in the patients with interstitial lung disease (*n* = 64). ΔX5: within-breath change in reactance at 5 Hz (expiratory X5 minus inspiratory X5). VC: vital capacity. DLco: diffusing capacity of carbon monoxide.

the calibre of the central airways. Pressure oscillation at high frequency is severely dampened before reaching the peripheral airways, but it penetrates much further into the lung periphery at low frequency. Thus, R5 reflects total respiratory resistance, whereas R20 reflects central airway resistance. The difference between R5 and R20 (R5 − R20) is thought to be an index of the small airways.[3] Based on these observations, R5, R20, and R5 − R20 results from ILD patients may suggest the presence of small airway disease[24]; however, these results were not distinguishable from those for obstructive lung diseases.[10] In addition, inspiratory−expiratory analyses of R5, R20, and R5 − R20 failed to discriminate ILD from obstructive lung diseases (Fig. 1A and B, Table 3). These results suggest that resistance measured using IOS cannot reveal the characteristics of ILD; however, inspiratory−expiratory analysis of reactance might show a distinctive pattern for ILD.

Although promising results were obtained, we are aware that this study has limitations. First, the number of the patients included in the study was relatively small. To verify the results, a larger sample size study is necessary. Secondly, for the data analysis, we used the raw values measured by IOS for various ages of subjects, since definitive predictive equations have not yet been established. Again, a large-scale study across a wider age range is needed to validate existing reference values.[9]

Conclusion

We have demonstrated that an increased magnitude of X5 during inspiration compared to X5 during expiration was a characteristic finding in inspiratory−expiratory analysis of IOS performed for patients with ILD. Significant inverse correlations between the magnitude of inspiratory−expiratory difference in X5 (ΔX5) and VC or DLco were observed, and these data may suggest an association between ΔX5 and severity and physiological abnormality in patients with ILD. ΔX5 results showed clearly different patterns among patients with asthma, COPD, and ILD. Exaggerated inspiratory reactance in ILD may reflect reduced distensibility and increased elastic recoil of the lung during inspiration, although further studies are needed to investigate its cause.

Acknowledgement

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2013.03.005.

Conflict of interest

The authors declare that they have no competing interests.

References

1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;**165**:277−304.
2. Thompson MJ, Colebatch HJ. Decreased pulmonary distensibility in fibrosing alveolitis and its relation to decreased lung volume. *Thorax* 1989;**44**:725−31.
3. Kubota M, Shirai G, Nakamori T, Kokubo K, Masuda N, Kobayashi H. Low frequency oscillometry parameters in COPD patients are less variable during inspiration than during expiration. *Respir Physiol Neurobiol* 2009;**166**:73−9.
4. Al-Mutairi SS, Sharma PN, Al-Alawi A, Al-Deen JS. Impulse oscillometry: an alternative modality to the conventional pulmonary function test to categorise obstructive pulmonary disorders. *Clin Exp Med* 2007;**7**:56−64.
5. MacLeod D, Birch M. Respiratory input impedance measurement: forced oscillation methods. *Med Biol Eng Comput* 2001;**39**:505−16.
6. Dellaca RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklem PT, Pedotti A, Calverley PM. Detection of expiratory flow limitation in COPD using the forced oscillation technique. *Eur Respir J* 2004;**23**:232−40.
7. Paredi P, Goldman M, Alamen A, Ausin P, Usmani OS, Pride NB, Barnes PJ. Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. *Thorax* 2010;**65**:263−7.
8. Kanda S, Fujimoto K, Komatsu Y, Yasuo M, Hanaoka M, Kubo K. Evaluation of respiratory impedance in asthma and COPD by an impulse oscillation system. *Intern Med* 2010;**49**:23−30.
9. Oostveen E, MacLeod D, Lorino H, Farre R, Hantos Z, Desager K, Marchal F. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003;**22**:1026−41.
10. van Noord JA, Clement J, Cauberghs M, Mertens I, Van de Woestijne KP, Demedts M. Total respiratory resistance and reactance in patients with diffuse interstitial lung disease. *Eur Respir J* 1989;**2**:846−52.
11. Fisher AB, DuBois AB, Hyde RW. Evaluation of the forced oscillation technique for the determination of resistance to breathing. *J Clin Invest* 1968;**47**:2045−57.
12. Obol BJ. Tests of ventilatory function not requiring maximal subject effort. II. The measurement of total respiratory impedance. *Am Rev Respir Dis* 1968;**97**:868−79.
13. Muller E, Vogel J. Measurement and model-interpretation of new parameters of lung mechanics (author's transl). *Z Erkr Atmungsorgane* 1981;**157**:340−4.
14. GINA Report. *Global strategy for asthma management and prevention.* http://www.ginasthma.org/; 2010.
15. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease.* http://www.goldcopd.org/; 2010.
16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319−38.
17. Society TJR, editor. *Spirometry, flow-volume curve, diffusion capacity of the lung.* Tokyo: The Japanese Respiratory Society; 2004.
18. Nishida O, Kannabe M, Sewake N, Takano M, Kawane H, Kodomari Y, Arita K, Nasuno H, Nishimoto Y. Pulmonary function in healthy subjects and its prediction: 5. Pulmonary diffusing capacity in adults. *Jpn J Clin Pathol* 1976;**24**:941−7.

19. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;**26**:720—35.

20. Kolsum U, Borrill Z, Roy K, Starkey C, Vestbo J, Houghton C, Singh D. Impulse oscillometry in COPD: identification of measurements related to airway obstruction, airway conductance and lung volumes. *Respir Med* 2009;**103**:136—43.

21. Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. *Lung* 2011;**189**:121—9.

22. Egan JJ, Martinez FJ, Wells AU, Williams T. Lung function estimates in idiopathic pulmonary fibrosis. the potential for a simple classification. *Thorax* 2005;**60**:270—3.

23. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. *Proc Am Thorac Soc* 2006;**3**:315—21.

24. Fulmer JD, Roberts WC. Small airways and interstitial pulmonary disease. *Chest* 1980;**77**:470—2.