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Analysis of respiratory function and respiratory impedance in elderly patients with fixed airflow obstruction

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Abstract

Objectives: Asthma and chronic obstructive pulmonary disease (COPD) are representative respiratory diseases characterized by obstructive ventilatory impairment. Asthma–COPD overlap syndrome (ACOS) has recently attracted attention. This study aimed to analyze the pathology of obstructive ventilatory impairment by assessment of respiratory function and impedance in smokers with fixed airflow obstruction, regardless of the disease entity.

Methods: Thirty-eight elderly patients with a minimum of a 10 pack-year smoking history and fixed airflow obstruction with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of <70% after bronchodilator administration were included. Respiratory function and impedance parameters were measured and compared across four phenotypes. Phenotypes were based on the pulmonary diffusing capacity and airway reactivity to inhaled bronchodilators. Groups 1 and 2 included carbon monoxide diffusion capacity (DLCO) <80% without and with positive airway reactivity, respectively. Groups 3 and 4 included DLCO ≥ 80% without and with positive airway reactivity, respectively.

Results: FEV1 (% predicted) was significantly correlated with lung resistance at 5 Hz (R5), 20 Hz (R20), and R5 − R20 in patients with fixed airflow obstruction. The correlation with R5 and R5 − R20 was stronger than that with R20. These results are similar to those reported for patients with COPD, and suggest that small airways are primarily affected in patients with fixed airflow obstruction. Group 2 patients tended to show lower FEV1/FVC and higher ΔX5 values than patients in the other groups.. In some Group 2 patients, FEV1 and respiratory impedance values improved after addition of or a dose increase in inhaled corticosteroids, and this suggested the presence of ACOS.

Conclusions: Evaluation of older patients with fixed airflow obstruction using various approaches is useful for determining the underlying pathology.

Keywords: Bronchial asthma, Chronic obstructive pulmonary syndrome, Asthma–chronic obstructive pulmonary disease overlap syndrome, Respiratory function, Respiratory impedance

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are representative respiratory diseases characterized by obstructive ventilatory impairment. Asthma is characterized by eosinophil-dominant, chronic inflammation in the large and small airways and reversible airway constriction.[1] However, COPD is characterized by neutrophil-dominant inflammation and involves specific histopathological changes. These changes typically include destruction of the lung parenchyma and thickening of the airway wall. COPD exhibits a mix of emphysema and airway lesions and causes airflow obstruction that is not fully reversible.[2] Although asthma and COPD are different diseases with different etiologies, they share many clinical symptoms. Differentiation between the two entities is difficult, particularly in elderly patients with a smoking history. Moreover, a certain number of patients may have both asthma and COPD. In recent years, asthma–COPD overlap syndrome (ACOS) has attracted attention as a condition exhibiting features of both diseases. Although various investigations have been performed, several aspects of this disease entity remain unclear.[1,2] Measurement of the pulmonary diffusing capacity has been reported to be useful for differentiating between asthma and COPD. Zeki et al. proposed that ACOS is defined by one of the following two phenotypes: (1) asthma with airway obstruction that is not completely reversible and a decreased carbon monoxide diffusion capacity (DLCO, % predicted; <80%); and (2) COPD with emphysema accompanied by reversible or partially reversible airflow obstruction.[3]

In the present study, we aimed to analyze the pathology of obstructive ventilatory impairment by assessment of respiratory function and respiratory impedance in ever smokers with fixed airflow obstruction, regardless of the disease entity. Additionally, we compared measurements among patients who were stratified into four phenotype groups based on the pulmonary diffusing capacity and airway reactivity to inhaled bronchodilators.

Methods

Study design

The subjects were outpatients at our department who reported a minimum smoking history of 10 pack-years and had fixed airflow obstruction with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of <70% after a bronchodilator challenge. Patients with any organic respiratory diseases other than emphysema were excluded. Based on these criteria, a total of 38 patients the median age was 75 years and most of the patients were men (n=36)., including 25 current

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smokers and 13 former smokers, were enrolled. Between April 2013 and March 2015, measurements of respiratory impedance and respiratory function test parameters were obtained. Chest computed tomography (CT) was also performed. The clinical diagnoses before initiation of the study were asthma in seven patients, COPD in 24, and ACOS in seven (Table 1). They were then classified into four phenotypes according to the diffusing capacity and airway reactivity in the same manner as reported by Zeki et al.[3] The reference value of DLCO (% predicted) was 80%. Airway reversibility was considered clinically significant at a 12% or greater improvement rate of FEV1 or improved amount of 200 ml or more.[4] However, because airway constriction is widely observed from central airways to peripheral airways, the extent of impairment is not uniform. In this study, we considered FEV1 and peak expiratory flow (PEF) as indicators of central airway impairment. We also considered maximum expiratory flow at 25% of the forced vital capacity (V25), the maximum midexpiratory flow rate (MMF), and the improvement rate of FEV1 after short-acting β_2-agonist (SABA) inhalation as indicators of peripheral airway impairment. Among the patients, 29 could undergo the airway reversibility test. These patients were classified into four phenotypes based on the diffusing capacity (DLCO, % predicted) and airway reactivity as follows: Group 1, DLCO <80% without positive airway reactivity; Group 2, DLCO <80% with positive airway reactivity; Group 3, DLCO ≥80% without positive airway reactivity; and Group 4, DLCO ≥80% with positive airway reactivity. We also added inhaled corticosteroid (ICSs) or increased the dose to evaluate the treatment effects for three Group 2 patients who provided consent. Consent from the other patients could not be obtained for increasing ICSs. The present study was approved by the Fujita Health University Ethics Review Committee (Approval No. HM16-023). All patients provided written informed consent prior to their study participation.

The Modified Medical Research Council (mMRC) scale was used to evaluate dyspnea in daily living, with a grading of 0 (only become short of breath with strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing).[5]

Measurements

Spirometric parameters, lung volume fractions, and diffusing capacities were measured using a pulmonary function test system (CHESTAC-8800; Chest M.I., Inc., Tokyo, Japan). Positive airway reactivity was defined as an increase in FEV1, PEF, V25/height, or MMF by 12% after inhalation of a bronchodilator. High-resolution CT scans of the chest at full inspiration were obtained using a 64-slice multidetector row CT device (Brilliance 64; Philips Electronics Japan Ltd., Tokyo, Japan). Automatic quantification of emphysema was performed using automatic software (Ziostation2; Ziosoft Inc., Tokyo, Japan). The extent of emphysema (% low attenuation areas) was estimated using the threshold technique by quantifying the percentage of the total lung voxels with an apparent X-ray attenuation value below –950 Hounsfield units. Respiratory impedance was measured using an impulse oscillation system (IOS; MasterScreen IOS, Erich Jaeger, Hoechberg, Germany).

Analysis

All statistical analyses were performed using StatFlex ver. 6.0 (Artech Co., Ltd., Osaka, Japan). Two independent groups were compared using the Mann–Whitney U test, while two paired groups were compared using Wilcoxon's test. The degree of association between two variables was determined using Spearman's rank correlation coefficients. Differences across three or more independent groups were assessed using the Kruskal–Wallis test. Values of $p < 0.05$ were considered to be statistically significant.

Results

The characteristics of the included patients are shown in Table 1. The median FEV1 (% predicted), FEV1/FVC ratio, and DLCO (% predicted) were 65.7%, 55.3%, and 84.0%, respectively.

The correlations of respiratory impedance parameters with age, body mass index, and respiratory function parameters are shown in Table 2. In patients with fixed airflow obstruction, FEV1 (% predicted) was significantly correlated with lung resistance at 5 Hz (R5; $\rho = -0.49$, $p = 0.002$ and 20 Hz (R20; $\rho = -0.32$, $p = 0.049$), and with the difference between R5 and R20 (R5 − R20; $\rho = -0.49$, $p = 0.0017$). The correlations of FEV1 with R5 and R5 − R20 appeared to be stronger than that with R20. FEV1 (% predicted) was significantly correlated with the difference between the mean expiratory and inspiratory reactance at 5 Hz (ΔX5; $\rho = -0.50$, $p = 0.002$), but not with the reactance at 5 Hz (X5; $\rho = 0.17$, $p = 0.31$). There were similar trends in the correlations of FEV1 (% predicted) with PEF (% predicted), V25/Ht (% predicted), and MMF (% predicted).

The characteristics of the patients stratified by phenotype are shown in Table 3. Groups 1, 2, 3, and 4 included six, eight, five, and 10 patients, respectively. The FEV1/FVC ratio, mMRC score, and ΔX5 were significantly different among the four groups (Table 3). Group 2 had the lowest FEV/FVC ratio and the highest mMRC score and ΔX5 (Table 3, Figure 1). This finding suggested that Group 2 patients might have had better airway reactivity and were more likely to be asthmatic component compared with Group 1 patients. Group 2 patients may have been receiving insufficient inhaled corticosteroids (ICSs) or inadequate treatment. We added ICSs or increased the dose to evaluate the treatment effects for three Group 2 patients who provided consent. The existing treatments for these three patients included a long-acting muscarinic antagonist (LAMA; tiotropium) for Patients 1 and 2 and an ICS/long-acting β_2 agonist (LABA; salmeterol/fluticasone compounds [SFC] 250) for Patient 3. Respiratory function and respiratory impedance parameters were compared before and after the 8-week intervention (addition or dose increase). All three patients had been diagnosed with COPD. Only Patient 3 received ICSs before intervention. Fluticasone 400 μg daily was added for Patients' 1 and 2. For Patient 3, SFC250 was switched to SFC500. Respiratory function and respiratory impedance parameters before and after intervention are shown in Figure 2. FEV1 was slightly improved in Patients' 1 and 3. With regard to respiratory impedance, R5 − R20 and ΔX5 showed a trend toward improvement in Patients 1 and 3.

Discussion

In the present study, we found that FEV1 (% predicted) was significantly correlated with R5, R20, and R5 − R20 in patients with fixed airflow obstruction. The correlations of FEV1 with R5 and R5 − R20 were stronger than that with

Table 1. Median and proportions of variables of older patients with fixed airway obstruction

Patients	N = 38
Age (years)	75.0 (72.0–79.8)
Sex	
Male	N = 36 (94.7%)
Female	N = 2 (5.3%)
BMI (kg/m2)	22.1 (20.1–24.1)
Current smoker	N = 25 (65.8%)
Clinical diagnosis	
Asthma	N = 7 (18.4%)
COPD	N = 24 (63.2%)
ACOS	N = 7 (18.4%)
mMRC score	2.0 (1.0–3.0)
LAA% (− 950 HU) (%)	6.2 (2.3–15.2)
FEV1 (% predicted)	65.7 (51.9–86.2)
FEV1/FVC	55.3 (48.7–65.0)
PEF (% predicted)	64.4 (40.0–79.6)
V25/Ht (% predicted)	13.7 (10.6–18.1)
MMF (% predicted)	18.6 (13.9–27.9)
DLCO (% predicted)	84.0 (61.8–103.4)
R5 (kPa/s/L)	0.29 (0.23–0.39)
R20 (kPa/s/L)	0.22 (0.18–0.26)
R5-R20 (kPa/s/L)	0.07 (0.04–0.12)
X5 (kPa/s/L)	− 0.14
(− 0.28 to − 0.10)	
Δ X5 (kPa/s/L)	0.03 (0.02–0.11)

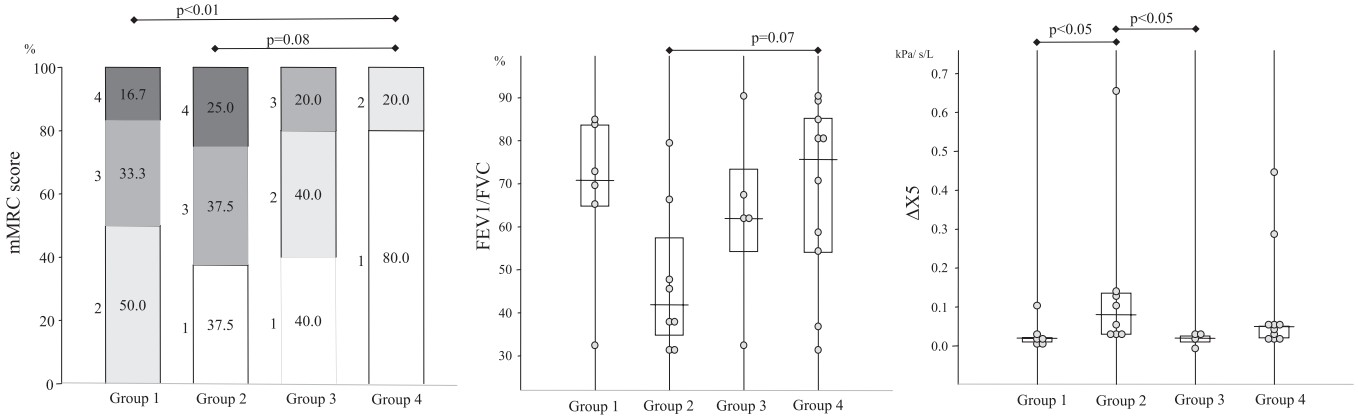
Values are presented as median (25th – 75th percentile) or numbers.
BMI: body mass index, COPD: chronic obstructive pulmonary disease, ACOS: asthma-COPD overlap syndrome, mMRC: Modified Medical Research Council, LAA: low attenuation areas, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: peak expiratory flow, V25: maximum expiratory flow at 25% of the forced vital capacity, MMF: maximum midexpiratory flow, DLCO: carbon monoxide diffusion capacity, R5: resistance at 5 Hz, R20: resistance at 20 Hz, R5−R20: difference between R5 and R20, X5: reactance at 5 Hz, Δ: difference between expiratory and inspiratory phases.

Table 2. Correlations among respiratory impedance and age, body mass index (BMI), and respiratory function in patients with chronic airflow obstruction

	ρ				
	R5	R20	R5 − R20	X5	Δ X5
Age (years)	0.06	− 0.22	0.25	− 0.22	0.15
BMI (kg/m2)	− 0.06	0.011	− 0.10	0.09	− 0.12
LAA% (−950 HU) (%)	− 0.09	− 0.10	− 0.08	− 0.05	0.33
FEV1 (% predicted)	− 0.49**	− 0.32*	− 0.49 †	0.17	− 0.50**
FEV1/ FVC	− 0.30	− 0.19	− 0.31	0.03	− 0.30
PEF (% predicted)	− 0.58 †	− 0.32	− 0.63 †	0.17	− 0.53**
V25/Ht (% predicted)	− 0.44**	− 0.28	− 0.45 †	0.18	− 0.43**
MMF (% predicted)	− 0.46**	− 0.29	− 0.47 †	0.17	− 0.42**
DLCO (% predicted)	0.09	− 0.10	0.10	0.77/0.08	− 0.16

*p < 0.05, **p < 0.01, † p < 0.001 (Spearman's rank correlation coefficients).
BMI: body mass index, mMRC: Modified Medical Research Council, LAA: low attenuation areas, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: peak expiratory flow, V25: maximum expiratory flow at 25% of the forced vital capacity, MMF: maximum midexpiratory flow, DLCO: carbon monoxide diffusion capacity, R5: resistance at 5 Hz, R20: resistance at 20 Hz, R5 − R20: difference between R5 and R20, X5: reactance at 5 Hz, Δ: difference between expiratory and inspiratory phases.

Figure 1.



Relevance of phenotype and mMRC score, FEV1/FVC, and Δ X5 in fixed airflow obstruction cases.
Patients were classified into four phenotypes based on the diffusing capacity (DLCO, % predicted) and airway reactivity as follows: Group 1, DLCO <80% without positive airway reactivity; Group 2, DLCO <80% with positive airway reactivity; Group 3, DLCO ≥ 80% without positive airway reactivity; Group 4, DLCO ≥ 80% with positive airway reactivity. Two-group comparisons were performed by the Mann-Whitney test (Bonferroni correction).
Group 2 had the lowest FEV/FVC ratio and the highest mMRC score and Δ X5.
mMRC: Modified Medical Research Council, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, X5: reactance at 5 Hz, Δ: difference between expiratory and inspiratory phases.

Table 3. Patients' characteristics and measurements according to phenotype

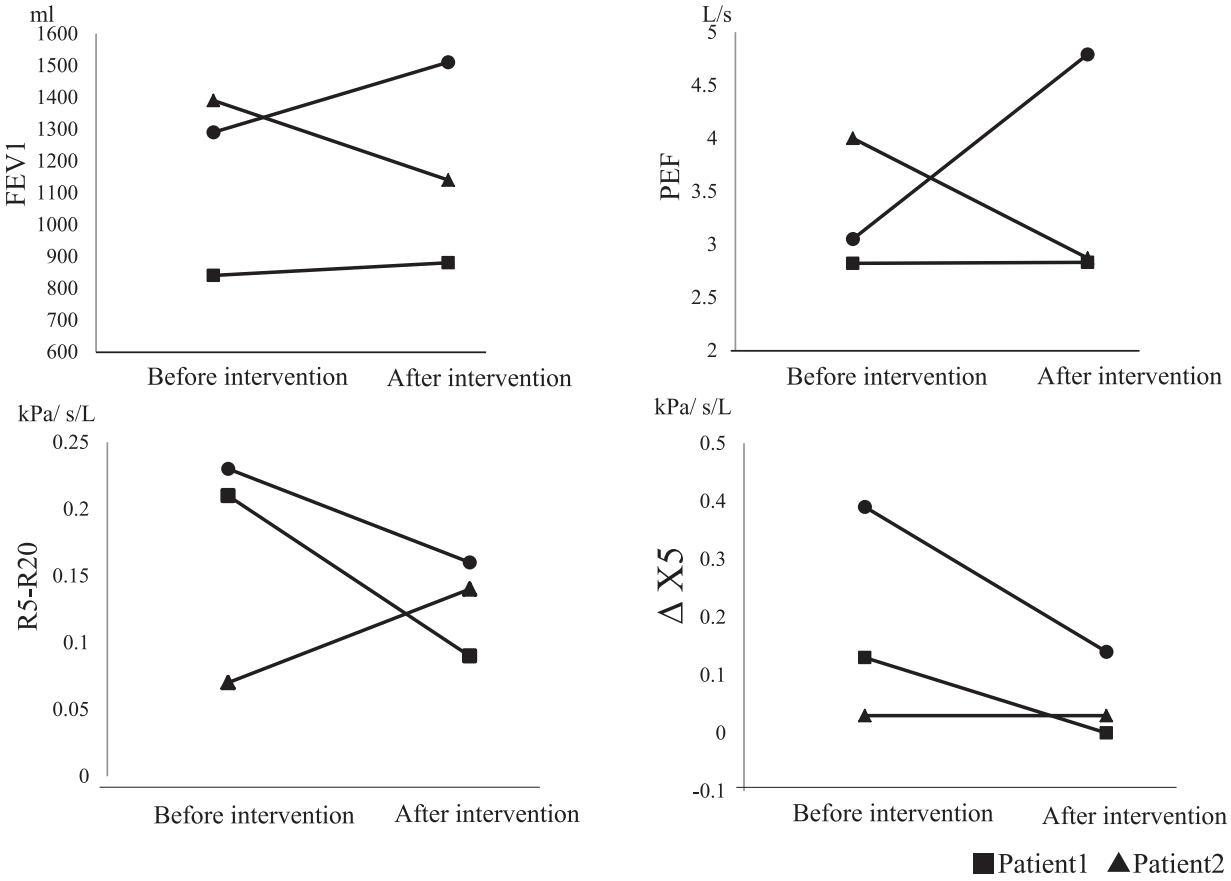
Patients		Group 1 (N = 6)	Group 2 (N = 8)	Group 3 (N = 5)	Group 4 (N = 10)
DLCO (% predicted)		<80%	<80%	≥ 80%	≥ 80%
Positive airway reactivity		Without	With	Without	With
Age (years)		75.5 (69.0–77.5)	73.5 (70.3–76.5)	73.0 (73.0–80.0)	76.0 (72.0–82.0)
Sex (male/female)		N = 5/1	N = 7/1	N = 5/0	N = 10/0
BMI (kg/m2)		21.6 (21.3–23.2)	19.3 (20.1–24.1)	20.1 (18.7–20.4)	23.8 (22.1–24.4)
Current smoker *		N = 1 (16.7%)	N = 1 (12.5%)	N = 0 (0%)	N = 5 (100%)
Clinical diagnosis	Asthma	N = 0 (0%)	N = 0 (0%)	N = 2 (40.0%)	N = 3 (30.0%)
	COPD	N = 4 (66.7%)	N = 6 (75.0%)	N = 3 (60.0%)	N = 4 (40.0%)
	ACOS	N = 2 (33.3%)	N = 2 (25.0%)	N = 0 (0%)	N = 3 (30.0%)
Treatment	ICS/LABA	N = 3 (50.0%)	N = 4 (50.0%)	N = 2 (40.0%)	N = 6 (60.0%)
	ICS	N = 1 (16.7%)	N = 1 (12.5%)	N = 1 (20.0%)	N = 1 (10.0%)
	LABA	N = 2 (33.3%)	N = 4 (50.0%)	N = 3 (60.0%)	N = 3 (30.0%)
	LAMA	N = 2 (33.3%)	N = 3 (37.5%)	N = 3 (60.0%)	N = 3 (30.0%)
	LABA/LAMA	N = 0 (0%)	N = 1 (12.5%)	N = 0 (0%)	N = 0 (0%)
	CS	N = 1 (16.7%)	N = 0 (0%)	N = 1 (20.0%)	N = 1 (10.0%)
mMRC score*		2.5 (2.0–3.0)	3.0 (1.0–3.3)	2.0 (1.0–2.0)	1.0 (1.0–1.0)
LAA% (− 950 HU) (%)		17.2 (2.9–30.5)	14.2 (6.7–18.3)	4.1 (2.4–19.4)	3.6 (1.9–6.1)
FEV1/FVC *		54.8 (51.0–60.8)	47.2 (40.7–53.7)	54.0 (52.3–54.2)	62.0 (57.0–66.3)
R5 (kPa/s/L)		0.27 (0.25–0.30)	0.42 (0.29–0.46)	0.3 (0.23–0.31)	0.23 (0.2–0.33)
R20 (kPa/s/L)		0.21 (0.19–0.24)	0.24 (0.21–0.34)	0.19 (0.19–0.19)	0.19 (0.17–0.24)
R5 − R20 (kPa/s/L)		0.05 (0.04–0.07)	0.12 (0.09–0.17)	0.04 (0.02–0.12)	0.04 (0.02–0.06)
X5 (kPa/s/L)		–0.13 (–0.17 to –0.10)	–0.18 (–0.27 to –0.14)	–0.12 (–0.24 to –0.12)	–0.12 (–0.42 to –0.10)
Δ X5 (kPa/s/L)*		0.02 (0.01–0.02)	0.08 (0.03–0.12)	0.02 (0.02–0.02)	0.05 (0.02–0.05)

Patients were classified into four phenotypes based on the diffusing capacity and airway reactivity as follows: Group 1, DLCO (% predicted) <80% without positive airway reactivity; Group 2, DLCO (% predicted) <80% with positive airway reactivity; Group 3, DLCO (% predicted) ≥ 80% without positive airway reactivity; Group 4, DLCO (% predicted) ≥ 80% with positive airway reactivity.
Values are presented as median (25th – 75th percentile) or numbers.
*$p < 0.05$ (Kruskal–Wallis test).
BMI: body mass index, COPD: chronic obstructive pulmonary disease, ACOS: asthma–COPD overlap syndrome, ICS: inhaled corticosteroids, LABA: long-acting β2 agonist, LAMA: long-acting muscarinic antagonist, CS: corticosteroids, mMR: Modified Medical Research Council, LAA: low attenuation areas, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, R5: resistance at 5 Hz, R20: resistance at 20 Hz, R5 − R20: difference between R5 and R20, X5: reactance at 5 Hz, Δ : difference between expiratory and inspiratory phases.

R20. These results are similar to those reported for patients with COPD[6-9] and suggest that small airways are primarily affected in patients with fixed airflow obstruction. With regard to patients with COPD, one study[6] showed a significant correlation between FEV1 and X5, whereas another reported no such correlation.[7] The present study also showed a lack of a significant correlation between FEV1 (% predicted) and X5 in patients with fixed airflow obstruction. We believe that the heterogeneous study sample, including patients with asthma, COPD, and ACOS, may have affected respiratory reactance. FEV1 (% predicted) was significantly correlated with ΔX5, an indicator of expiratory airflow limitation.[10,11]

We further classified our patients into four phenotype groups based on the diffusing capacity and airway reactivity. We found that Group 2 (DLCO <80% with positive airway reactivity) patients tended to had the lowest FEV/FVC ratio and the highest mMRC score and ΔX5 values than patients in the other groups. Patients with ACOS reportedly show more severe disease, a worse quality of life, a higher mortality rate, and a more rapid decline in lung function compared with patients with asthma or COPD alone.[12,13] Most of the patients who were prediagnosed with COPD in Group 2 were likely to have ACOS. The reason for the higher percentage of current smokers in Group 4 is unknown. Respiratory function and airway responsiveness were maintained in Group 4 patients compared with patients in other groups. Therefore, exacerbation of symptoms by smoking might not have been homogeneous across individuals, and some patients who were less sensitive to smoking could have continued smoking.[14] Two patients in Group 2 showed improved FEV1 values and respiratory impedance after the addition of or a dose increase in ICSs. Fingleton et al. performed cluster analysis in 389 subjects with complaints of wheezing and shortness of breath related to airflow obstruction.[15] They found that the effects of ICSs were the strongest in Group 3 (adult-onset ACOS), as indicated by St. George's Respiratory Questionnaire scores and changes in airflow limitation.[15] Patients who had been diagnosed with COPD before initiation of the present study may actually have had ACOS and may have responded to ICSs. The Global Initiative for Asthma (2015) and Global Initiative for Chronic Obstructive Lung Disease (2016) guidelines recommend intensive treatment with ICSs.[1,2] A larger study is necessary to determine the pathology of fixed airway obstruction.

Figure 2.



Respiratory function and respiratory impedance parameters before and after intervention of added or increased inhaled corticosteroids in patients in Group 2. Respiratory function and respiratory impedance parameters were compared before and after 8 weeks of intervention (addition or dose increase). Fluticasone 400 μg daily was added for Patients' 1 and 2. For Patient 3, SFC250 was switched to SFC500. FEV1 was slightly improved in Patients' 1 and 3. With regard to respiratory impedance, R5 − R20 and Δ X5 showed a trend toward improvement in Patients' 1 and 3.
FEV1: forced expiratory volume in 1 second, PEF: peak expiratory flow, R5: resistance at 5 Hz, R20: resistance at 20 Hz, R5 − R20: difference between R5 and R20, X5: reactance at 5 Hz, Δ : difference between expiratory and inspiratory phases.

Because the present study only included elderly patients, whether our findings can be applied to adult general patients is unclear. Additionally, elderly patients with asthma with a longstanding history reportedly have more severe airflow limitation and less complete reversibility than late-onset elderly patients with asthma.[16] Therefore, disease duration should be considered in future studies together with widening the target age.

Conclusions

Our results suggest that evaluation of elderly patients with fixed airflow obstruction using various approaches is useful for determining further details regarding the underlying pathology and selecting optimal treatment strategies. Further investigations are warranted to confirm our findings.

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Conflicts of Interest

None

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