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Original Paper

A comparative study of asthma with airflow limitation and asthma-COPD overlap using the forced oscillation technique

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Abstract

The forced oscillation technique (FOT), which requires breathing without forced action, is a useful tool that can measure respiratory impedance. We investigated the physiological differences between asthma with smoking-unrelated airflow limitation and asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) using the FOT. Among 275 patients with asthma who presented at the Showa University Hospital from April 2018 through March 2019, 211 were enrolled and assigned into the asthma (BA), asthma with airflow limitation (AL), or ACO groups. Respiratory impedance measured using the FOT were compared among the groups. There were no significant differences in spirometry data between the AL and the ACO group. The AL group had higher respiratory resistance at 5 Hz (R5), 20 Hz (R20), and reactance at 5 Hz than the ACO group, but there was no significant difference in subtracting R20 from R5 (R5-R20). R5 and R20 were similar between the ACO and the BA groups, but R5-R20, resonant frequency (Fres), and low-frequency reactance area were significantly higher in the ACO group than the BA group. Fres yielded the highest area under the curve (AUC) to identify airflow limitation, and R20 yielded the highest AUC to identify the ACO group among patients with airflow limitation. An analysis using the cut off value to identify airflow limitation and ACO detected 33 patients as having ACO, 17 of whom were diagnosed with ACO. R5 and R20 measured by FOT are higher in AL than in ACO despite no difference in spirometry data, and are not significantly different between BA and ACO. Therefore, FOT aids our understanding of the physiological characteristics and provides clues for the treatment in asthmatics with airflow limitation.

Key words: forced oscillation technique, asthma and COPD overlap, respiratory resistance, airflow limitation

Introduction

Asthma is characterised by eosinophil-based chronic airway inflammation and reversible airflow limitation, defined by a sustained decrease in a forced expiratory volume in 1 second / forced vital capacity (FEV_1 / FVC : FEV_1%) of < 70%. Airflow limitation in asthma is commonly due to contraction of airway smooth muscle and structural changes such as increased thickness and fibrosis of the airway smooth muscle, which may cause irreversible obstruction[1, 2]. Currently, the prevention and treatment of airflow limitation remains a challenge for clinicians[3].

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Abbreviations: ACO, asthma-COPD overlap; ACT, asthma control test; AL, asthma with airflow limitation; ALX, low-frequency reactance area; AUC, area under the curve; BA, asthma; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; IgE, Immunoglobulin E; ROC, receiver operating characteristic; Rrs, respiratory system resistance; R5, respiratory system resistance at 5 Hz; R5-R20, subtracting R20 from R5; R20, respiratory system resistance at 20 Hz; Xrs, respiratory system reactance; X5, reactance at 5 Hz; Zrs, respiratory system impedance

In asthma, the airflow limitation causes dyspnea on exertion, and its treatment and management remain a challenge to this day. In Japan, asthma patients whose airflow limitation is thought to be induced by tobacco smoke are diagnosed with asthma-COPD overlap (ACO)[4]. However, some asthmatic patients develop airflow limitation and exhibit clinical signs and symptoms similar to COPD patients such as dyspnea on exertion, despite not smoking or having smoked only a small amount. Understanding the pathophysiology of this development of airflow limitation is important for proper application of treatment modalities and avoidance of persistent airflow limitation.

The forced oscillation technique (FOT) can assess both proximal and peripheral airway dynamics by taking advantage of the low frequencies that propagate down the small airways[5]. Because it requires breathing without forced action, the FOT is a helpful tool that can measure respiratory impedance (Zrs) for people who have difficulty with spirometry, such as those with decreased lung function, the elderly, and children[6-8]. The FOT is a non-invasive procedure that uses sine waves at 2–3 simultaneous frequencies to measure the lung mechanics shown by Zrs. Respiratory resistance (Rrs), measured by FOT, is the real part of Zrs, while respiratory reactance (Xrs) is the theoretical part of Zrs[9]. Rrs includes resistance at 5 Hz (R5), 20 Hz (R20), and subtracting R20 from R5 (R5–R20), while Xrs include reactance at 5 Hz (X5), low-frequency reactance area (ALX), and resonant frequency (Fres). The explanations of each parameters are shown in Table 1[9-12].

Mori *et al*. demonstrated the potential for the FOT to differentiate between COPD and asthma patients, and that more differences between the inspiratory and expiratory X5 (ΔX5) were observed in COPD than in asthma[13]. A previous study showed that the FOT pattern of asthmatics included a moderately high Zrs over the entire frequency range when compared with healthy subjects[14]. Another study showed a further negative change in X5 during expiration in severe COPD patients, whereas no significant changes were observed in healthy never-smokers and asthma patients, even in patients with $FEV_1\% < 70\%$[10]. The difference in the FOT results between asthma with airflow limitation and ACO is not fully understood. We conducted a retrospective study using the FOT to determine the differences in asthma, asthma with airflow limitation, and ACO.

Methods

Study design and patients

We conducted a single-center, retrospective, case-control study. Data were collected from 275 patients with asthma who presented at Showa University Hospital (Tokyo, Japan) from April 2018 through March 2019. Of these, 64 patients were excluded because they had no FOT data during the previous year. The remaining 211 patients were divided into three groups: the asthma (BA, n = 67), asthma with airflow limitation (AL, n = 78), and ACO (n = 66). Patient data were retrospectively reviewed to obtain clinical characteristics, including diagnosis, age, sex, body weight, height, body mass index (BMI), smoking history, and laboratory data. A diagnosis of asthma was made on a patient's history and symptoms, based on the Global Initiative for Asthma[15]. BMI was calculated as weight in kilograms divided by the square of the height in meters. ACO was diagnosed based on the "Asthma and COPD overlap diagnosis and treatment guideline 2018"[4]. Patients with asthma who showed persistent airflow limitation ($FEV_1\% < 70\%$ after inhalation of short-acting β2 agonists), but did not meet the criteria for ACO diagnosis were categorised into the AL group. The protocol was approved by the ethics committee of Showa

Table 1. FOT parameters

Abbr	Full name	Interpretation
Zrs	respiratory impedance	including Rrs, Xrs[9]
Rrs	respiratory resistance	reflecting airway diameter, including R5 and R20[10]
Xrs	respiratory reactance	reflecting elasticity of lung, including X5, Fres, ALX[10]
R5	respiratory resistance at 5 Hz	resistance of entire airway[11,12]
R20	respiratory resistance at 20 Hz	resistance of large airway[11,12]
R5–R20	subtracting R20 from R5	resistance of small airway[11,12]
X5	respiratory reactance at 5 Hz	elastic recoil in the peripheral airways[11]
Fres	resonant frequency	elastic recoil in the peripheral airways[11]
ALX	low-frequency reactance area	elastic recoil in the peripheral airways[11]

Abbr, abbreviation.

University School of Medicine (Approval number: 3272), and informed consent was obtained in the form of opt-out on the web-site. This study was performed in accordance with the principles of the Declaration of Helsinki.

Spirometry

Respiratory function in all subjects was assessed using a spirometer (CHESTAC-8900, Chest MI, Inc., Tokyo, Japan). The forced expiration maneuvre was conducted while the subject was in a standing position. Predicted values for FEV_1 and FVC were derived using local reference data from the Japanese Respiratory Society[16].

FOT

Zrs values were evaluated using FOT (Mostgraph-01, Chest MI, Inc., Tokyo, Japan) in all subjects, and all assessments were performed by a trained laboratory technologist. In cases where both respiratory function tests were to be performed at the same time, FOT was performed before spirometry to avoid bronchospasm caused by intense exhalation and inspiration. The subjects were instructed to sit, slightly extend their neck, and to place the mouthpiece in their mouth and make sure that there is no space between the lips and mouthpiece. All subjects wore nose clips and held their cheeks firmly with their hands during the impedance measurement. The measurement was performed three times, in succession, and the best results were used. We accepted resting tidal volumes of coherence of at least 0.7 and excluded values when resting tidal volumes were unstable due to coughing, swallowing, vocalization, and breath holding[11].

Fractional exhaled nitric oxide (FeNO)

FeNO, which indicates airway eosinophilic inflammation[17], was measured using a portable device (NIOX MINO, Aerocrine AB, Solna, Sweden) at an expiratory flow rate of 50 ml / s for 10 s.

Statistical analyses

The results are expressed as the mean ± standard error of the mean for continuous variables. All analyses were performed using JMP system version 14 (SAS Institute Inc., Cary, NC, USA). The differences in continuous variables were analyzed using the Kruskal-Wallis test. Differences between two groups were evaluated using the Mann-Whitney U test with Bonferroni's post-hoc correction. The differences in categorical variables were analyzed using Pearson χ^2 tests. To detect ACO using FOT in patients with $FEV_1\% < 70\%$, receiver operating characteristic (ROC) curves were analyzed[18, 19]. The value that maximizes sensitivity-(1-specificity) was set as the cut off value. A value of $P < 0.05$ was considered statistically significant. In the case of Bonferroni's post-hoc test, a value of $P < 0.017$ (a level of significance of alpha $= 0.017 = 0.05 / 3$) was considered statistically significant.

Results

Patients

Table 2 shows the characteristics of the study patients. There were no significant differences in BMI, eosinophil count, *Dermatophagoides pteronyssinus* specific Immunoglobulin E (IgE), and asthma control test (ACT) scores between the groups. The mean age was younger in the BA group than the other two groups (vs AL, $P < 0.001$; vs ACO, $P < 0.001$) and more patients were male in the ACO group than the other two groups (vs BA, $P < 0.001$; vs AL, $P < 0.001$). Smoking frequency and status were significantly higher in the ACO group than in the other two groups, but no different between the BA and AL groups. FeNO levels and total IgE were not significantly different between the AL and the ACO groups. There were no significant differences in medication step, the number of inhaled corticosteroids users, and the number of long-acting beta-agonist users between the groups. More patients were administered STEP1 medication in the ACO group than in the other groups (BA, AL, ACO; 3.0%, 2.5%, 10.6%; respectively). Long-acting muscarinic antagonist users were higher in the ACO group than in the other groups (BA, AL, ACO; 7.5%, 17.9%, 50.0%; respectively). The number of biologic users, who were using omalizumab, mepolizumab, benralizumab, or dupilumab, was significantly higher in the AL group than in the ACO groups (AL, ACO; 20.5%, 6.0%; respectively).

Spirometry data

Spirometry data are shown in Table 3. There were no significant differences in %FVC between the groups. No significant differences were observed in all variables except for FVC and peak expiratory flow rate, which were not adjusted by gender, age and height, between the AL and ACO groups. BA group had a higher $\%FEV_1$ than the AL and ACO groups (vs AL, $P < 0.001$; vs ACO, $P < 0.001$), but there was no significant difference between the AL and ACO groups ($P = 0.151$). All variables except for FVC were significantly different between the BA and AL groups.

Table 2. Characteristics of the 211 patients with BA, AL, and ACO

Characteristics	BA (n=67)	AL (n=78)	ACO (n=66)	*P*-value		
				BA vs AL	BA vs ACO	AL vs ACO
Age : years	54.2±14.6	65.5±13.5	66.8±11.3	< 0.001*	< 0.001*	0.812
Male : n (%)	20 (29.8)	29 (37.1)	54 (81.8)	0.276	< 0.001*	< 0.001*
BMI : kg/m^2	23.2±4.2	23.2±3.0	23.8±3.1	-	-	-
Smoking frequency : pack-years	3.2±9.4	0.8±2.1	38.9±30.6	0.766	< 0.001*	< 0.001*
Smoking status C/Ex/N : n (%)	3 (4.5) / 9 (13.4) / 55 (82.1)	2 (2.5) / 12 (15.3) / 64 (82.0)	5 (7.5) / 61 (92.4) / 0	0.788	< 0.001*	< 0.001*
cedar pollinosis : n (%)	51 (76.1)	39 (50.0)	11 (16.6)	0.001*	< 0.001*	0.051
Eosinophil count : /μl	290±228	479±455	320±236	-	-	-
IgE : IU/mL	878.4±2747.4	675.9±1105.5	1156.1±1859.1	0.403	0.003*	0.021
Der p-specific IgE positive : n (%)	39 (58.2)	39 (50.0)	32 (48.4)	-	-	-
FeNO : ppb	45.9±40.5	62.6±49.0	54.5±41.5	0.006*	0.178	0.349
ACT : point	21.1±3.6	20.7±3.6	20.2±3.1	-	-	-
Medication step : n (%)	2 (3.0) / 11 (16.4) / 20 (29.9) / 24 (35.8) / 10 (14.9)	2 (2.5) / 7 (8.9) / 29 (37.1) / 19 (24.3) / 21 (26.9)	7 (10.6) / 2 (3.0) / 31 (46.9) / 20 (30.3) / 6 (9.0)	-	-	-
Biologics : n (%)	6 (9.0)	16 (20.5)	4 (6.0)	0.049	0.526	0.011*
ICS : n (%)	65 (97.0)	76 (97.4)	59 (89.3)	-	-	-
LABA : n (%)	51 (76.1)	62 (79.4)	60 (90.9)	-	-	-
LAMA : n (%)	5 (7.5)	14 (17.9)	33 (50.0)	0.063	< 0.001*	< 0.001*

BA, asthma ; AL, asthma with airflow limitation ; ACO, asthma-COPD overlap ; BMI, body mass index ; C, current smoker ; Ex, ex-smoker ; N, never smoker ; Der p, *Dermatophagoides pteronyssinus* ; IgE, Immunoglobulin E ; FeNO, fractional exhaled nitric oxide ; ACT, asthma control test ; ICS, inhaled corticosteroids ; LABA, long-acting beta-agonists ; LAMA, long-acting muscarinic antagonist. Values are mean ± standard error of the mean. *P < 0.017

Table 3. Comparisons of variables measured by spirometry between BA, AL, and ACO

Parameters	BA (n=67)	AL (n=78)	ACO (n=66)	*P*-value		
				BA vs AL	BA vs ACO	AL vs ACO
FVC, L	3.13±0.82	2.93±0.86	3.42±0.87	0.133	0.062	0.002*
%FVC, %predicted	102.3±17.7	102.0±15.7	102.2±18.8	-	-	-
FEV_1, L/sec	2.48±0.70	1.73±0.60	1.91±0.67	< 0.001*	< 0.001*	0.130
%FEV_1, %predicted	97.3±15.4	74.8±16.5	70.8±20.6	< 0.001*	< 0.001*	0.151
FEV_1%, %predicted	79.2±6.5	58.6±8.24	55.8±11.3	< 0.001*	< 0.001*	0.384
PEF, L/s	7.16±1.90	5.29±1.91	6.03±1.90	< 0.001*	0.006*	0.016*
V50, L/s	2.19±1.21	0.98±0.49	1.06±0.63	< 0.001*	< 0.001*	0.782
%V50, %	79.9±26.6	30.7±12.5	30.4±16.5	< 0.001*	< 0.001*	0.659
V25, L/s	0.88±0.63	0.23±0.13	0.24±0.14	< 0.001*	< 0.001*	0.444
%V25, %	59.6±28.8	21.2±10.7	20.2±10.2	< 0.001*	< 0.001*	0.466
V50/V25	3.94±1.43	4.56±1.71	4.31±1.45	0.015*	0.086	0.429

BA, asthma; AL, asthma with airflow limitation; ACO, asthma-COPD overlap; FVC, forced vital capacity; %FVC, %forced vital capacity; FEV_1, forced expiratory volume in 1 second; %FEV_1, % forced expiratory volume in 1 second; FEV_1%, forced expiratory volume in 1 second / forced vital capacity; PEF, peak expiratory flow rate; V50, Expiratory flow at 50% lung volume; V25, Expiratory flow at 25% lung volume. Values are mean ± standard error of the mean. *P < 0.017

Table 4. Comparisons of variables measured by FOT between BA, AL, and ACO

Parameters	BA (n=67)	AL (n=78)	ACO (n=66)	*P*-value		
				BA vs AL	BA vs ACO	AL vs ACO
R5 AVE : $cmH_2O/l/s$	3.49±1.61	4.50±1.64	3.73±1.26	< 0.001*	0.102	0.005*
R20 AVE : $cmH_2O/l/s$	2.85±1.07	3.38±1.05	2.83±0.83	< 0.001*	0.697	0.001*
R5-R20 AVE : $cmH_2O/l/s$	0.63±0.63	1.12±0.67	0.90±0.52	< 0.001*	0.001*	0.060
X5 AVE : $cmH_2O/l/s$	−0.66±0.92	−1.66±1.60	−1.04±1.05	< 0.001*	0.004*	0.015*
Fres AVE : Hz	8.39±3.60	12.9±5.44	11.2±4.67	< 0.001*	< 0.001*	0.054
ALX AVE : $cmH_2O/l/s$ x Hz	3.79±7.87	11.9±15.2	7.26±8.84	< 0.001*	0.001*	0.433

FOT, forced oscillation technique; BA, asthma; AL, asthma with airflow limitation; ACO, asthma-COPD overlap; AVE; average; R5, respiratory system resistances at 5 Hz; R20, respiratory system resistances at 20 Hz; R5-R20, subtracting R20 from R5; X5, respiratory system reactance at 5 Hz; Fres, resonant frequency; ALX, low-frequency reactance area. Values are mean ± standard error of the mean. *P < 0.017

FOT

Average Zrs levels as measured by FOT are shown in Table 4. All variables were significantly higher in the AL group than in the BA group. The ACO group had significantly higher Xrs (X5, Fres, and ALX) and R5-R20 than the BA group. However, R5 and R20 were not significantly different between the groups. The AL group had higher R5, R20, and X5 values than the ACO group, but no significant difference was observed in R5-R20 between the groups. Based on these results, R5 and R20 at the expiratory and inspiratory phases were compared between the AL and ACO groups. R5 was significantly higher in the AL group than in the ACO group in the inspiratory phase and the average phase (R5 AVE, $P < 0.001$; R5 In, $P = 0.005$) (Figure 1A, C). There were no significant differences in any phase of R5 between the BA and ACO groups (Figure 1A, B, C). In all phases, R20 was significantly higher in the AL group than in the ACO group (R20 AVE, $P = 0.001$; R20 In, $P = 0.010$; expiratory R20, $P < 0.001$) (Figure 1D, E, F). There were no significant differences in any phase of R20 between the BA and ACO groups (Figure 1D, E, F). These results indicate that the patients in the AL group have a more proximal airway obstruction than those in the ACO group. Table S1 shows the differences between the inspiratory and expiratory phases of Zrs (ΔZrs). There were significant differences in ΔXrs (ΔX5, ΔFres, and ΔALX), but there were no significant differences either in ΔRrs (ΔR5, ΔR20, and ΔR5-R20) between the three groups. No significant differences were observed in any ΔXrs between the AL and ACO groups.

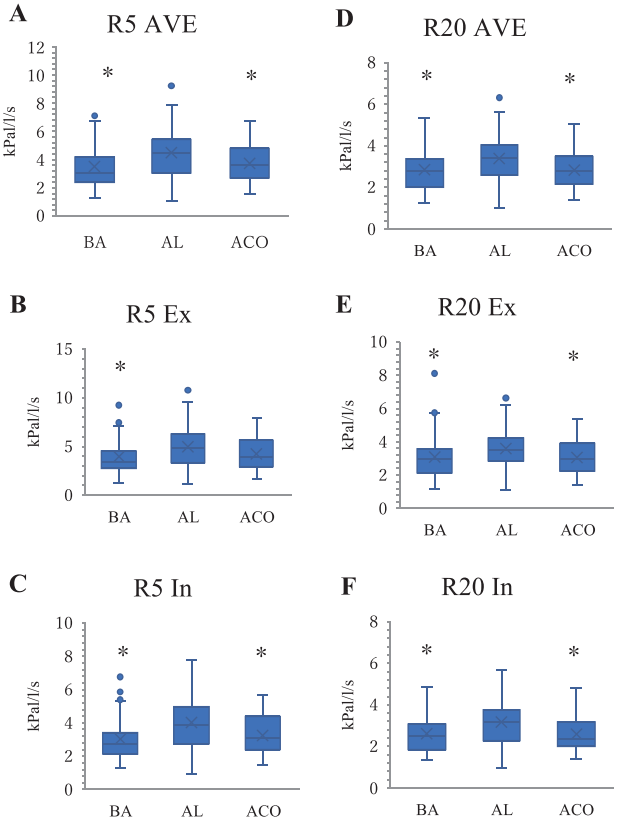

Fig. 1. Comparisons of R5 and R20 among BA, AL and ACO groups

Average R5 (A), expiratory R5 (B), inspiratory R5 (C), average R20 (D), expiratory R20 (E), and inspiratory R20 (F) were measured by FOT. Comparisons among the three groups were made with the Kruskal-Wallis test. Comparisons between two groups were made with Mann-Whitney U test with Bonferroni's post-hoc correction. R5, respiratory system resistances at 5 Hz; R20, respiratory system resistances at 20 Hz; BA, asthma; AL, asthma with airflow limitation; ACO, asthma-COPD overlap; AVE; average; Ex, expiratory; In, inspiratory. *P < 0.017 vs AL.

Supplement material

Table S1. Comparisons of the differences between inspiratory and expiratory Zrs between BA, AL, and ACO

Parameters	BA (n=67)	AL (n=78)	ACO (n=66)	*P*-value		
				BA vs AL	BA vs ACO	AL vs ACO
ΔR5 : cmH_2O/l/s	0.944±0.954	0.971±0.999	1.00±0.902	-	-	-
ΔR20 : cmH_2O/l/s	0.476±0.528	0.410±0.607	0.467±0.582	-	-	-
ΔR5-R20 : cmH_2O/l/s	0.479±0.485	0.560±0.533	0.526±0.425	-	-	-
ΔX5 : cmH_2O/l/s	−0.271±1.11	−1.01±1.92	−0.698±1.32	0.002*	0.007*	0.7003
ΔFres : Hz	1.11±3.31	2.97±3.81	2.58±3.96	< 0.001*	0.011*	0.4249
ΔALX : cmH_2O/l/s x Hz	2.96±11.8	10.4±19.6	6.70±12.4	< 0.001*	0.001*	0.427

Zrs, respiratory impedance; Ex, expiratory; In, inspiratory; BA, asthma; AL, asthma with airflow limitation; ACO, asthma-COPD overlap; R5, respiratory system resistances at 5 Hz; R20, respiratory system resistances at 20 Hz; R5-R20, subtracting R20 from R5; X5, respiratory system reactance at 5 Hz; Fres, resonant frequency; ALX, low-frequency reactance area. Values are mean ± standard error of the mean. *P < 0.017

Table 5. Accuracy of variables measured by FOT for identification of FEV_1% < 70% in 211 patients with BA, AL, and ACO

Parameters	AUC	Confidence interval	cut off	*P*-value	Sensitivity	Specificity	PPV	NPV
R5 AVE : cmH_2O/l/s	0.646	0.563-0.721	4.19	0.005*	0.500	0.776	0.827	0.419
R20 AVE : cmH_2O/l/s	0.598	0.514-0.676	3.01	0.072	0.555	0.656	0.776	0.407
R5-R20 AVE : cmH_2O/l/s	0.695	0.614-0.766	0.77	< 0.001*	0.625	0.746	0.841	0.480
X5 AVE : cmH_2O/l/s	0.698	0.619-0.767	−0.78	< 0.001*	0.569	0.761	0.836	0.451
Fres AVE : Hz	0.724	0.648-0.789	10.71	< 0.001*	0.569	0.791	0.854	0.460
ALX AVE : cmH_2O/l/s x Hz	0.707	0.629-0.775	6.66	0.001*	0.423	0.895	0.897	0.419

FOT, forced oscillation technique; FEV_1%, forced expiratory volume in 1 second/ forced vital capacity; BA, asthma; AL, asthma with airflow limitation; ACO, asthma-COPD overlap; AUC, area under the curve; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; R5-R20, subtracting R20 from R5; X5, respiratory system reactance at 5 Hz; Fres, resonant frequency; ALX, reactance area; PPV, positive predicted value; NPV, negative predicted value. Values are mean ± standard error of the mean. *$P < 0.05$.

Association between FOT and FEV_1% < 70%

Since FOT does not require forced maximal breathing, it will be beneficial for people who experience dyspnea during forced breathing, such as in COPD patients. ROC curve analysis of the FOT variables was used to identify airflow limitation. The accuracy of the FOT variables for the identification of FEV_1% < 70% is shown in Table 5. Fres yielded the highest AUC value (0.724), making it the most closely associated variable with an FEV_1% < 70%. The optimum cut off frequency was 10.71 Hz, with 56.9% sensitivity and 79.1% specificity. The positive predictive value was 85.4% and the negative predictive value was 46.0%.

Association between FOT and ACO

ROC curve analysis of FOT variables was used to identify ACO in patients with an FEV_1% < 70%. The accuracy of the FOT variables is shown in Table 6. Although there were a few differences in AUC, R20 yielded the highest AUC value (0.654) with statistically significant differences, suggesting that it was the variable most closely associated with ACO. The optimum cut off point was 3.33 kPa/l/s, with 71.2% sensitivity and 56.4% specificity. The positive predictive value was 58.0%, and the negative predictive value was 69.8%.

Detection of ACO by FOT

The results of ACO detection using Fres and the R20 cut-off point obtained in this study are shown in Figure 2. We first used Fres for detection of FEV_1% < 70%, followed by R20 for detection of ACO. There were 96 patients with Fres ≥ 10.71 Hz (BA, AL, ACO : n = 14, n = 47, n = 35, respectively), 82 (85.4%) of whom were FEV_1% < 70%. Of the 96 patients, 33 had an R20 ≤ 3.33 kPa/l/s (BA, AL, ACO : n = 6, n = 10, n = 17, respectively) and were assigned to

Table 6. Accuracy of variables measured by only FOT for identification of ACO in 144 patients with FEV_1% < 70%

Parameters	AUC	Confidence interval	cut off	*P*-value	Sensitivity	Specificity	PPV	NPV
R5 AVE : cmH_2O/l/s	0.634	0.281–2.32	4.12	0.02*	0.636	0.628	0.591	0.671
R20 AVE : cmH_2O/l/s	0.654	0.536–2.91	3.33	< 0.001*	0.712	0.564	0.580	0.698
R5–R20 AVE : cmH_2O/l/s	0.590	−0.197–1.10	1.48	0.029	0.893	0.294	0.517	0.766
X5 AVE : cmH_2O/l/s	0.617	−0.171–0.789	−0.48	0.011	0.439	0.782	0.630	0.622
Fres AVE : Hz	0.593	−0.216–1.50	7.83	0.045	0.363	0.807	0.615	0.600
ALX AVE : cmH_2O/l/s x Hz	0.597	−0.286–0.563	1.89	0.023	0.439	0.756	0.604	0.614

FOT, forced oscillation technique; ACO, asthma-COPD overlap; AUC, area under the curve; FEV_1%, forced expiratory volume in 1 second / forced vital capacity; AVE; average; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; R5–R20, subtracting R20 from R5; X5, respiratory system reactance at 5 Hz; Fres, resonant frequency; ALX, reactance area; PPV, positive predicted value; NPV, negative predicted value. Values are mean ± standard error of the mean. *$P < 0.05$.

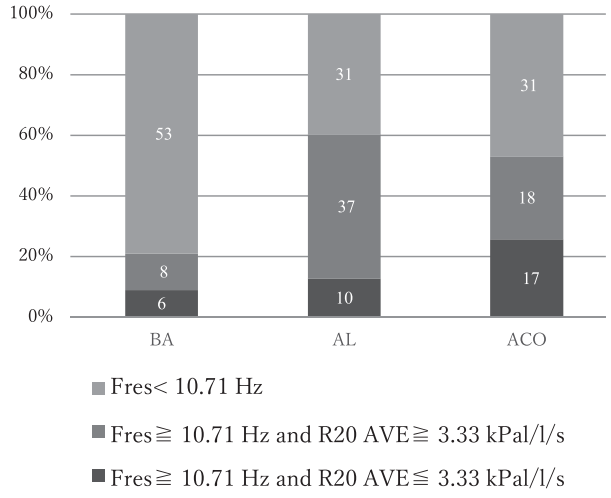

Fig. 2. Distribution of the patients classified by the cut off point of Fres and R20
Patients were differentiated by the cut off point of Fres 10.71 Hz to identify FEV_1% < 70%, and then the patients whose Fres was higher than 10.71 Hz were differentiated by the cut off point of R20 3.33 kPa/l/s to identify ACO. Numbers in each bars were absolute numbers of patients. ACO, asthma-COPD overlap; AVE, average; Fres, resonant frequency; R20, respiratory system resistance at 20 Hz.

ACO, 17 of whom were diagnosed with ACO. The positive predictive value was 51.5%.

Discussion

This study investigated the physiological differences in FOT results in patients with asthma, asthma with airflow limitation, and ACO. R5, R20 and X5 were significantly increased in the AL group compared with those in the ACO group, but no significant difference was observed in R5–R20 between these groups. Although most of the FOT variables showed higher airway resistance in the ACO group than in the BA group, R5 and R20 were similar between these groups.

It is important to determine the differences in FOT results to investigate the physiological differences between patients with different types of asthma, particularly when multiple types involve obstructive pulmonary function. Zrs was higher in patients with asthma than in healthy subjects and was positively correlated with pulmonary function[14]. In this study, the degree of airflow limitation measured by spirometry was similar between the AL and ACO groups, whereas most of the FOT variables, particularly R5, R20, and X5, were higher in the AL group compared with the ACO group. A previous study conducted by Kitaguchi *et al*. showed the similar tendencies that Rrs values were higher in asthma patients with airflow limitation compared with ACO patients[20]. These data suggest there is higher respiratory resistance, at least Rrs, in AL patients than those in ACO patients. A prospective research with a larger number of patients is needed to confirm this hypothesis.

A previous study reported that R20 correlates with proximal airway resistance, and R5–R20 correlates with peripheral airway resistance[12]. We showed that R5 and R20, but not R5–R20, were significantly higher in the AL group than the ACO group, suggesting that the AL group had higher proximal airflow limitation than the ACO group. By using FOT, this study revealed that airflow limitation occurred at a more proximal location in the AL group. Since inhaled drugs, which are the main treatment for asthma, reaches different parts of the airway depending on its particle size, it may be possible to prevent future airflow limitation by selecting the inhaled drug according to the obstructed part of the airway. Additionally, although most of the FOT

variables had higher respiratory resistance in the ACO group than in the BA group, R5 and R20 were similar. This finding suggests that smoking exposure tends to induce obstructive changes in distal airways but not proximal airways, at least, in patients with asthma.

Previous studies showed that ΔX5 was useful in differentiating between COPD and asthma[12]. However, there were no significant differences in ΔXrs between the AL and ACO groups, suggesting that ΔXrs could not differentiate between AL and ACO in the clinical setting.

The AL group had significantly worse spirometry and FOT data than the BA group. However, there was no significant difference in ACT scores and medication steps. A previous study reported that airflow limitation developed despite sufficient treatment, suggesting that anti-asthma medications might have minimal effects on airway remodeling, specifically in older patients with asthma[3]. Meanwhile, 90% of the AL group received at least step 3 treatment, and more than 50% of the AL group received at least step 4 treatment or more. The prevalence of patients using biologics such as omalizumab, mepolizumab, benralizumab, and dupilumab, was highest in the AL group. Thus, lower pulmonary function and higher Zrs in the AL group were not associated with insufficient treatment.

Fres had the highest correlation coefficient with FEV_1% in this study, which is consistent with previous reports showing that Fres is strongly associated with airflow limitation[21, 22]. This study had a comparatively high positive predictive value and low sensitivity, resulting from the low Fres cut-off point used. For the detection of airflow limitation, Fres measured by FOT, which does not require forced breathing, could be a substitute for spirometry. Fres has typically high values in children, and decreases with age, and tends to increase in both obstructive and restrictive disorders[11]. One reason for the low Fres cut-off point in this study might be that many elderly patients were included. In addition, the Fres cut-off point for $FEV_1\% < 70\%$ would depend on the disease profiles within the population. Therefore, background characteristics including age and disease profiles should be considered when determining Zrs cut-off values.

Our study has identified a few limitations. First, this was a single-center retrospective study and the sample size was relatively small. To confirm our hypothesis, a study with a large number of patients would be needed. Second, all participants in this study were patients with asthma. If the population included non-asthmatics, such as COPD patients and healthy control individuals, the Zrs cut off values for identification of $FEV_1\% < 70\%$ would be different. Third, previous report showed that low FEV_1 in early adulthood is associated with the genesis of COPD[23]. In the patients with the AL group in this study, it is possible that the airflow limitation is caused by pulmonary growth disorder in early adulthood as well as COPD. From the viewpoint of prevention of airflow limitation, it is necessary to examine the difference between the AL group and the ACO group regarding the longitudinal change of FOT data. Fourth, since this study was retrospective, computed tomography (CT) image data were insufficient, hence, a comparative study among the three groups was not possible. The relationship between FOT data and airway diameter and emphysematous change obtained from CT images are uncertain.

In conclusion, high R20 values measured by FOT were revealed to be the primary characteristic for the AL patients, compared with the ACO patients. Moreover, no differences were observed in R20 between the BA and ACO patients. Thus, FOT aids our understanding of the physiological characteristics and provides clue for treatment in asthmatics with airflow limitation.

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Conflict of interest disclosure

The authors have no conflict of interest to declare.

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