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Letter to the Editor

Forced oscillation technique may identify asthma-COPD overlap



Dear Editor,

As some patients have clinical features of both asthma and chronic obstructive pulmonary disease (COPD), asthma-COPD overlap (ACO) has recently been proposed as a diagnosis.^{1,2} Clinically, it can be difficult to distinguish asthma from COPD, especially in smokers and older adults. ACO is heterogeneous and includes different phenotypes, including asthma with irreversible airway obstruction due to smoking and COPD with eosinophilic airway inflammation. In our previous report,³ we showed that the combined assessment of serum periostin, a biomarker of type 2 inflammation in asthma, and serum YKL-40, a useful biomarker of COPD, may be beneficial for identifying ACO. To explore another useful biomarker, we focused on the forced oscillation technique (FOT). The FOT is used to measure respiratory system resistance (Rrs) and reactance (Xrs) during tidal breathing and provides information that cannot be obtained by spirometry.⁴ We hypothesized that FOT could differentiate ACO from asthma and COPD and assessed the usefulness of FOT for diagnosing ACO in this cross-sectional study.

The study subjects included 344 adult patients who visited outpatient clinics at Shizuoka General Hospital or Nihon University Itabashi Hospital for routine check-ups between February 2013 and August 2016. The participants were classified into three groups: asthma (n = 170), COPD (n = 60), and ACO (n = 114). The asthma and COPD patients fulfilled the definition of the Global Initiative for Asthma (GINA)¹ and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,² respectively. According to our previous report,³ ACO was diagnosed as shown in [Supplementary Figure 1](#). The syndromic diagnosis of ACO^{1,2} was not used because it is less objective.

On the examination day, the study subjects underwent FOT and spirometry in that order. The details are shown in [Supplementary Methods](#).

The flow and clinical characteristics of the subjects are shown in [Supplementary Figure 1](#) and [Table 1](#). Of the 114 patients with ACO, 85 were derived from asthma and 29 were derived from COPD. These patients differed from the simple overlap of both disease criteria: asthma patients with FEV1/FVC <0.7 and ≥ 10 pack-years (n = 63), and COPD patients with a history of asthma alone (n = 8). The ACO patients were older and male-dominant, had more pack-years, lower FEV1, FEV1/FVC, and X5, and higher R5–R20, $\Delta X5$, Fres, Δ Fres, ALX, and Δ ALX than the asthma patients. The ACO patients were younger, had higher body mass index and FEV1/FVC, and fewer pack-years than the COPD patients. Typical colored 3-dimensional images of Rrs and Xrs for each representative patient are shown in [Supplementary Figure 2](#). Recursive partitioning

analysis to create a classification tree revealed that $\Delta X5$, R20, ALX, and Fres were the significant parameters ([Supplementary Fig. 3, Table 2](#)). Classes 3 and 4 consisted predominantly of ACO patients. The accuracy of the diagnosis of ACO (class 3 and class 4) was as follows: diagnostic odds ratio, 3.47 (95% confidence interval, 1.98 to 6.09); sensitivity, 32%; and specificity, 88%.

To ensure the reliability of the definition of ACO in this study and to confirm the utility of FOT for its identification, we re-evaluated patients if they met the “asthma criteria” used in the definition of ACO for asthma patients and the “COPD criteria” for COPD patients. With this re-evaluation, 42 patients were excluded ([Supplementary Fig. 4](#)), but reanalysis of the remaining 302 patients (140 with asthma, 59 with COPD, and 103 (74 + 29) with ACO) yielded comparable results ([Supplementary Fig. 5, Supplementary Table 1](#)).

This study found that the FOT, the combined assessment of Rrs and Xrs, may be useful for identifying ACO. Recursive partitioning analysis revealed that $\Delta X5$, R20, ALX, and Fres were the significant parameters. Previous studies indicated that $\Delta X5$ best reflects the expiratory flow limitation (EFL), a major determinant of dynamic hyperinflation and exercise limitation in COPD patients.⁵ $\Delta X5$ is referred to as the EFL index and is useful for the differentiation between COPD and asthma.⁶ A significantly higher value of $\Delta X5$ in ACO and COPD patients suggests the presence of EFL compared to asthma patients. ACO patients showed the medium value of R20 between asthma and COPD patients. A previous study found that R20 had clinical significance, including severity, impaired control, quality of life, and frequent exacerbation of asthma.⁷ R20 seems to reflect the characteristics of asthma rather than those of COPD. Previous studies indicated that Xrs values, including Fres and ALX, were higher in COPD patients than in asthma patients.^{4,6} Comparable levels of Fres and ALX between ACO and COPD patients, but higher than in asthma patients, suggest the presence of COPD components in ACO patients. Overall, the combined assessment of Rs and Xrs led to the identification of ACO with high specificity despite low sensitivity. The diagnostic accuracy of this study was comparable to that of the combined assessment of serum periostin and YKL-40 (both high levels): diagnostic odds ratio, 2.59 (95% confidence interval, 1.58 to 4.25); sensitivity, 38%; and specificity, 81%.³ One of the limitations of our study was the definition of ACO. Since there is currently no consensus on the definition of ACO, we gave weight to the heavy smoking history or the presence of emphysema for asthma patients. For patients with COPD, we set a past history of asthma, atopy, blood eosinophil counts, and FeNO levels to capture allergic and non-allergic eosinophilic asthma. However, the reliability of this definition was not perfect, especially for asthma features in COPD patients. The uncertainty may be related to the ambiguity of the primary diagnosis of asthma or COPD because of the heterogeneous nature and subsequent difficulty in distinguishing

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Table 1
Characteristics of the subjects.

	Asthma (n = 170)	ACO (n = 114)	COPD (n = 60)	P value*
Age (years)	59 (42, 70) ^{†‡}	69 (61, 75) [§]	74 (69, 78)	<0.001
Gender (male/female)	51/119 ^{†‡}	89/25	48/12	<0.001
Body mass index (kg/m ²)	23 (21, 26) [†]	23 (21, 25) [§]	21 (19, 23)	<0.001
Pack-years	0 (0, 1) ^{†‡}	30 (12, 48) [§]	44 (26, 68)	<0.001
FEV1 (% predicted)	92.4 (80.1, 103.0) ^{†‡}	71.3 (52.1, 85.3)	66.9 (48.7, 85.6)	<0.001
FEV1/FVC (%)	73.8 (67.8, 79.7) ^{†‡}	58.9 (45.9, 65.6) [§]	50.8 (43.2, 59.1)	<0.001
R5 (cmH ₂ O/L/s)				
Whole-breath	3.58 (2.87, 4.34)	3.56 (2.92, 4.47)	3.30 (2.62, 4.03)	0.372
ΔR5	0.51 (0.24, 1.05)	0.47 (0.19, 0.86)	0.45 (0.21, 1.05)	0.627
R20 (cmH ₂ O/L/s)				
Whole-breath	2.98 (2.43, 3.49) [†]	2.83 (2.25, 3.37)	2.54 (1.97, 3.07)	0.011
ΔR20	0.21 (0.06, 0.54)	0.20 (0.05, 0.48)	0.18 (−0.01, 0.44)	0.512
R5–R20 (cmH ₂ O/L/s)				
Whole-breath	0.60 (0.30, 1.00) [†]	0.81 (0.48, 1.12)	0.81 (0.153, 1.08)	0.008
Δ (R5–R20)	0.28 (0.14, 0.54)	0.30 (0.09, 0.55)	0.28 (0.06, 0.58)	0.828
X5 (cmH ₂ O/L/s)				
Whole-breath	−0.63 (−1.30, −0.33) ^{†‡}	−1.06 (−1.85, −0.39)	−1.04 (−2.45, −0.61)	0.001
ΔX5	0.04 (−0.13, 0.30) ^{†‡}	0.30 (−0.04, 1.02)	0.45 (0.08, 1.00)	<0.001
Fres (Hz)				
Whole-breath	8.50 (6.93, 12.96) ^{†‡}	11.93 (7.42, 15.44)	12.72 (8.69, 17.40)	<0.001
ΔFres	0.19 (−0.62, 1.89) ^{†‡}	1.19 (−0.24, 3.54)	1.95 (0.49, 4.15)	<0.001
ALX (cmH ₂ O/L/s x Hz)				
Whole-breath	2.40 (1.07, 6.59) ^{†‡}	5.35 (1.37, 12.23)	5.50 (2.22, 17.33)	<0.001
ΔALX	0.19 (−0.41, 1.87) ^{†‡}	1.88 (−0.13, 8.72)	2.78 (0.52, 8.94)	<0.001

Data are shown as median (interquartile range) or frequency. *Kruskal–Wallis test. †P value < 0.017 asthma vs ACO (Mann–Whitney U test with Bonferroni adjustment, with a level of significance of alpha = 0.017 = 0.05/3). ‡P value < 0.017 asthma vs COPD. §P value < 0.017 ACO vs COPD. ACO, asthma–COPD overlap; ALX, low-frequency reactance area; COPD, chronic obstructive pulmonary disease; Δ, difference between inspiratory and expiratory phases; FEV1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz, respectively; X5, respiratory system reactance at 5 Hz.

Table 2
Diagnostic accuracy of asthma, ACO, and COPD using the recursive partitioning algorithm.

Class	Diagnosis	Diagnostic odds ratio (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
1	Asthma	3.52 (2.24, 5.51)	72 (64, 78)	58 (50, 66)	1.71 (1.40, 2.09)	0.49 (0.37, 0.64)
2	Asthma	1.78 (0.95, 3.35)	17 (12, 24)	90 (84, 94)	1.65 (0.95, 2.86)	0.93 (0.85, 1.01)
3	ACO	3.59 (1.57, 8.20)	14 (8, 22)	96 (92, 98)	3.23 (1.51, 6.89)	0.90 (0.83, 0.97)
4	ACO	2.67 (1.34, 5.32)	18 (11, 26)	93 (88, 96)	2.37 (1.29, 4.35)	0.89 (0.81, 0.98)
5	COPD	8.45 (3.42, 20.88)	22 (12, 34) ^E	97 (94, 99)	6.84 (3.06, 15.26)	0.81 (0.71, 0.93)
6	COPD	19.36 (6.05, 61.91)	22 (12, 34)	99 (96, 100)	15.38 (5.20, 45.55)	0.79 (0.70, 0.91)
1 + 2	Asthma	7.25 (4.13, 12.72)	89 (83, 93)	48 (40, 55)	1.70 (1.46, 1.98)	0.23 (0.15, 0.37)
3 + 4	ACO	3.47 (1.98, 6.09)	32 (23, 41)	88 (83, 92)	2.69 (1.72, 4.20)	0.78 (0.68, 0.89)
5 + 6	COPD	15.94 (7.49, 33.93)	43 (31, 57)	95 (92, 98)	9.47 (5.17, 17.33)	0.59 (0.48, 0.74)

ACO, asthma–COPD overlap; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

between the two diseases. This uncertainty may be the reason for inconsistency in the results of previously published studies. Further, there are two pathways to ACO: it may be derived from asthma or from COPD. However, this study alone did not determine whether ACO is a simple mixture of the two diseases or a more complex condition. Further studies are warranted to define ACO and to validate the role of FOT in identifying ACO in clinical practice.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.01.002>.

Conflict of interest

TS reports personal fees from AstraZeneca Japan outside of the submitted work. YG reports personal fees from AstraZeneca Japan and Boehringer Ingelheim outside of the submitted work. The rest of the authors have no conflict of interest.

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