Journal of Asthma and Allergy

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ORIGINAL RESEARCH

Assessment of Airway Remodeling Using Endobronchial Ultrasound in Asthma-COPD Overlap

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Purpose: The aim of this study was to evaluate the structural changes of the airways using the endobronchial ultrasound (EBUS) in ACO patients compared to severe asthma and COPD patients.

Patients and Methods: The study included 17 patients with ACO, 17 patients with COPD and 33 patients with severe asthma. Detailed clinical data were obtained from all participants. Basic laboratory tests were performed, including measurement of eosinophil counts in blood and serum immunoglobulin E (IgE) concentrations. All patients underwent spirometry and bronchoscopy with EBUS (a 20-MHz ultrasound probe) to measure the total thicknesses of the bronchial walls and their particular layers in segmental bronchi of the right lower lobe. EBUS allows to distinguish five layers of the bronchial wall. Layer 1 (L_1) and layer 2 (L_2) were analyzed separately, while the outer layers (layers 3–5 [L_{3-5}]) that correspond to cartilage were assessed together.

Results: In patients with ACO the thicknesses of the L_1 and L_2 layers, which are mainly responsible for remodeling, were significantly greater than in patients with COPD and significantly smaller than in patients with severe asthma (median L_1= 0.17 mm vs 0.16 mm vs 0.18 mm, $p<0.001$; median L_2= 0.18 mm vs 0.17 mm vs 0.20 mm, $p<0.001$, respectively). The thicknesses of the total bronchial walls ($L_1+L_2+L_{3-5}$) and L_{3-5} were significantly smaller in ACO and COPD patients compared to asthma patients (median $L_1+L_2+L_{3-5}$= 1.2 mm vs 1.14 mm vs 1.31 mm, $p<0.001$; median L_{3-5}= 0.85 mm vs, 0.81 mm vs 0.92 mm, $p=0.001$, respectively).

Conclusion: The process of structural changes in the airways assessed by EBUS is more advanced in individuals with ACO compared to patients with COPD, and less pronounced compared to patients with severe asthma. It seems that EBUS may provide useful information about differences in airway remodeling between ACO, COPD and severe asthma.

Keywords: asthma-COPD overlap, airway remodeling, total bronchial wall, bronchial wall layers, endobronchial ultrasound

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are recognized as a significant health, economic and social problem due to their high incidence and healthcare costs.[1] Asthma and COPD are characterized as separate disease entities with different clinical characteristics, pathophysiological mechanisms and strategy of treatment. However, some patients appear to have features of both diseases, which is termed asthma-chronic obstructive pulmonary disease overlap (ACO).[2] In line with the GINA and GOLD guidelines, ACO has been defined as a disease

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Received: 12 February 2021
Accepted: 30 April 2021
Published: 14 June 2021

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entity characterized by persistent bronchial obstruction in which both asthma and COPD features coexist.[3,4] There are no universal, validated criteria for the diagnosis of ACO, which renders a conduct of large, multicenter studies challenging in this population.[5]

Airway remodeling is fairly broadly defined as any change in the composition, distribution, thickness, weight, volume, or number of structural components in the bronchial wall in patients as compared to healthy subjects.[6] It is generally accepted that the airway remodeling is important in the development of both asthma and COPD.[7,8] There is a growing body of evidence that remodeling also plays a significant role in the pathogenesis of ACO.[9,10] Structural changes in the airways can be assessed in histopathological examinations of specimens from the bronchial mucosa and using imaging tests such as high-resolution computed tomography of the chest (HRCT),[11] endobronchial optical coherence tomography[12,13] or endobronchial ultrasound (EBUS).[14,15] EBUS may be used to evaluate the staging of non-small cell lung cancer and in the diagnosis of peripheral lesions, but it also allows to distinguish 5 layers of the bronchial wall in the cartilaginous bronchi.[16] Studies have shown that EBUS is useful in measuring the thicknesses of the bronchial walls and their individual layers in patients with asthma and COPD.[15,17,18] According to a thorough review of the available literature, EBUS has not been used so far to evaluate the remodeling in patients with ACO.

The aim of this study was to assess the structural changes of the airways using endobronchial ultrasound in subjects with ACO compared to patients with severe asthma and COPD.

Patients and Methods

Study Design

This prospective observational study was conducted from June 2016 to July 2020 and included 17 patients with ACO, 17 patients with COPD and 33 patients with severe asthma, aged 40–85 years, who were treated at the Pulmonology Clinic of the 2nd Department of Internal Medicine of the Jagiellonian University Medical College, Krakow, Poland. Patients remained without any exacerbation of the disease or respiratory tract infections in the 4 weeks preceding inclusion to the study. The diagnoses of ACO, COPD and severe asthma were consistent with the criteria of the GINA and/or GOLD reports.[19,20] Persistent airflow limitation was present in all ACO patients. According to the GINA/GOLD ACO criteria, we analyzed 11 separate features of asthma and COPD. ACO was diagnosed in patients presenting with at least 3 features of each disease and the number of features for asthma and COPD had to be similar. The diagnostic ACO criteria of the GINA/GOLD reports are presented in Table 1. COPD was diagnosed in patients, who met all criteria: physician-diagnosed COPD, persistent airflow limitation in spirometry (post bronchodilator $FEV_1/FVC < 70\%$), exposure to cigarette smoke (≥10 pack years of smoking history), presence of ≥3 of 11 features for COPD and <3 of 11 features for asthma in the GINA/GOLD ACO criteria and no asthma diagnosis before the age of 40 years. Severe asthma was diagnosed in patients, who fulfilled all criteria: physician-diagnosed asthma, <10 pack years of smoking history, ≥3 of 11 features for asthma and <3 of 11 features for COPD in the GINA/GOLD ACO criteria and disease remains uncontrolled despite GINA step 4 or 5 treatment or requires such treatment to maintain good symptom control and reduce the risk of exacerbations. The patients continued their current pharmacological treatment, except for the need to discontinue bronchodilators prior to pulmonary function tests according to the criteria of the GINA and GOLD reports. The study protocol was complied with Helsinki Declaration and its amendments and was approved by the Ethics Committee of Jagiellonian University Medical College, Kraków, Poland (KBET 122.6120.137.2016). Written informed consent was obtained from all participants.

Study Sample and Data Collection

A structured questionnaire was used to collect data including: demographic (age, sex) and detailed clinical information about subjects (symptoms, duration of the disease, diagnosis of lung disease before the age of 40, number and type of disease exacerbations, atopy status, comorbidities, medications, smoking status and occupational exposure). The severity of the disease and symptoms control were assessed using the Asthma Control Test (ACT), the COPD Assessment Test (CAT) and the Modified Medical Research Council Dyspnea Scale (mMRC scale). Basic laboratory tests (eosinophil counts in blood and immunoglobulin E [IgE] concentrations) were carried out. Spirometry was performed before and after the administration of a short-acting β_2-agonist to assess bronchial reversibility (Jaeger Master Screen, Höchberg, Germany).

Bronchoscopy was carried out according to ATS guidelines[21] under local anesthesia (2% lidocaine) and

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conscious sedation (0.05–0.1 mg intravenous fentanyl + 2.5–5.0 mg intravenous midazolam) by the same experienced pulmonologist using bronchofiberoscope BF-190 (Olympus, Tokyo, Japan). EBUS was performed with the use of a 20-MHz ultrasound probe (Olympus, Tokyo, Japan) cooperating with the EU-ME1 processor (Olympus, Tokyo, Japan). The probe was introduced through the working channel of the bronchofiberoscope to the orifices of the apical (RB6), anterobasal (RB8), lateral basal (RB9), and posterobasal (RB10) segmental bronchi of the right lower lobe. EBUS allows to distinguish five layers of the bronchial wall. The inner layers of the bronchial wall (layer 1 [L_1] and layer 2 [L_2]) containing the epithelium, submucosa and smooth muscles were analyzed separately, while the outer layers (layers 3–5 [$L_{3–5}$]) that correspond to cartilage were assessed together. The layers L_1, L_2 and $L_{3–5}$ together represent the entire thickness of the bronchial wall. The images selected from the video recorded during bronchoscopy were saved as bitmaps and were imported to the FES software (Feature Extraction Software, AGH University of Science and Technology in Kraków) for further analysis.

From the digital film sequences recorded during bronchoscopy, five frames were selected from each orifice in which the multilayered structure of the bronchial wall was best visible. The FES software was designed to process images, including converting data from the raster to vector format using the subpixel precision method. The borders of the individual layers were selected manually on each of the five frames by one experienced researcher, blinded to the diagnoses of patients. Selected images were magnified four to eight times. The distance between the two points was then measured and converted into millimeters using FES software. From five measurements of each layer, the mean was calculated and used in the statistical analysis. Outline of bronchial wall layers and schematic measurement of their thickness in EBUS in a patient with ACO are presented in Figure 1.

Statistical Analysis

The statistical analysis was performed in the R program, version 3.6.3. (R Core Team 2019, Vienna, Austria). The distribution of variables was assessed using the Shapiro–Wilk test. The quantitative and qualitative variables were presented as median (interquartile range) and number (percentage) respectively, unless otherwise specified. The categorical variables were compared using the χ^2 test (with Yates's correction for 2×2 tables) or the Fisher's exact test depending on the expected frequencies, while the comparison of continuous variables was performed using the Mann–Whitney test or the Kruskal–Wallis test, depending on the number of compared groups. Post-hoc analysis was carried out using Dunn's test. Correlations between continuous variables were analyzed using the Spearman's rank correlation test. A p value of less than 0.05 was considered statistically significant.

Results

ACO and COPD patients were older than those with asthma (median 66 vs 69 vs 55 years, respectively, $p<0.001$). The study groups did not differ significantly in terms of sex and body mass index (BMI). Diagnosis of the respiratory disease before the age of 40 was established more frequently among asthma and ACO patients than COPD patients (54.55% vs 41.18% vs 0%, respectively, $p=0.001$). ACO and COPD subjects had a greater number of pack-years than asthma subjects (median 30 vs 30 vs 0 pack-years, respectively, $p<0.001$). Clinical characteristics of all subjects are presented in Table 2.

ACO and COPD subjects were administered significantly lower daily doses of ICSs compared to asthma subjects (median 400 µg vs 400 µg vs 1000 µg fluticasone equivalent, respectively, $p=0.01$). Comparison of the percentage and the total number of eosinophils in the peripheral blood revealed no significant differences between the studied groups. High IgE concentration defined as ≥100 IU/mL (47.06% vs 54.55% vs 11.76%, respectively, $p=0.013$) and a history of atopy (29.41% vs 45.45% vs 0%, respectively, $p=0.003$) were significantly more frequent in ACO and asthma patients than in COPD patients. According to the diagnostic criteria of the disease, persistent airflow limitation was present in all COPD and ACO patients, while it was present in 45.45% of asthma patients ($p<0.001$). ACO and asthma subjects had similar FEV_1 values expressed in liters and as a percentage of predicted value in pre- and post-bronchodilator spirometry, while COPD patients were characterized by a significantly more severe degree of bronchial obstruction compared to the other two groups. The treatment, laboratory test results and spirometry parameters of all subjects are presented in Table 3.

The median thicknesses of the bronchial walls and their individual layers in ACO patients were, respectively: $L_1 + L_2 + L_{3–5} = 1.2$ mm, $L_1 = 0.17$ mm, $L_2 = 0.18$ mm and $L_{3–5} = 0.85$ mm. The thicknesses of the L_1 and L_2 layers in ACO subjects were significantly greater than in COPD

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Table 1 GINA/GOLD Criteria of ACO Diagnosis[19,20]

More Likely Asthma If	More Likely COPD If
1. Onset < age 20 years	1. Onset > age 40 years
2. Variation in symptoms within short periods	2. Persistence of symptoms
3. Worsening of symptoms at night/early morning	3. Daily symptoms with and exertional dyspnea with good/bad days
4. Symptoms trigerred by exercise, emotions/laughter, dust, or exposure to allergens	4. Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
5. Documented airflow limitation variability (peak flow, spirometry)	5. Documented persistent airflow limitation (post bronchodilator FEV_1/FVC < 70%)
6. Lung function normal between symptoms	6. Lung function abnormal between symptoms
7. Previous doctor diagnosis of asthma	7. Previous doctor diagnosis of COPD, chronic bronchitis, or emphysema
8. Family history of asthma or atopy/eczema	8. Heavy exposure to a risk factor (tobacco smoke, biomass fuel)
9. No worsening of symptoms over time. Symptoms vary either seasonally or from year to year	9. Symptoms slowly worsening over time (progressive course over years)
10. May improve spontaneously or have an immediate response to bronchodilators or to inhaled steroids over weeks	10. Rapid-acting bronchodilator treatment provides only limited relief
11. Chest X-ray normal	11. Chest X-ray with features of severe hyperinflation

Abbreviations: GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

subjects and significantly smaller than in asthma subjects (median L_1= 0.17 mm vs 0.16 mm vs 0.18 mm, respectively, p<0.001; median L_2= 0.18 mm vs 0.17 mm vs 0.20 mm, respectively, p<0.001). In contrast, the thicknesses of the total bronchial walls ($L_1 + L_2 + L_{3–5}$) and the layers corresponding to the cartilage ($L_{3–5}$) were significantly smaller in ACO and COPD patients compared to asthma patients (median L_1+L_2+$L_{3–5}$= 1.2 mm vs 1.14 mm vs 1.31 mm, respectively, p<0.001; median $L_{3–5}$= 0.85 mm vs, 0.81 mm vs 0.92 mm, respectively, p=0.001). The exact results are presented in Table 4, Figures 2 and 3. Among ACO patients, there were no differences between the GOLD groups and the total thicknesses of the bronchial walls as well as their particular layers (L_1+L_2+$L_{3–5}$, p=0.209; L_1, p= 0.756; L_2, p= 0.205; $L_{3–5}$, p=0.32). Similarly, COPD subjects were characterized by the similar total thicknesses of the bronchial walls and their particular layers among the GOLD groups (L_1+L_2+$L_{3–5}$, p=0.617; L_1, p= 0.983; L_2, p=0.386; $L_{3–5}$, p=0.57). The thickness of total bronchial wall (L_1+L_2+$L_{3–5}$) and thickness of the layers corresponding to cartilage ($L_{3–5}$) correlated negatively with MEF50% (r=−0.629, p=0.009 and r=−0.602, p=0.014, respectively) and MEF25% (r=−0.57, p=0.021 and r=−0.577, p=0.019, respectively). The thicknesses of the bronchial walls and their individual layers did not correlate with FEV_1, the disease duration, the degree of disease control assessed in the ACT test, the severity of symptoms in the CAT test and mMRC scale, or the ICSs doses in ACO patients. Detailed data are presented in Table 5. There were no serious complications after bronchoscopy with EBUS. The EBUS slightly extended the duration of the procedure and therefore patients required more sedatives. Several patients presented a transient rise in body temperature after bronchoscopy.

Discussion

In this prospective observational study, we observed significant differences between ACO, COPD and severe asthma patients in terms of the thicknesses of the total bronchial walls and their individual layers. These results suggest that EBUS could be a useful tool in the differentiation of ACO, COPD and severe asthma. According to a thorough review of the available literature, we could not

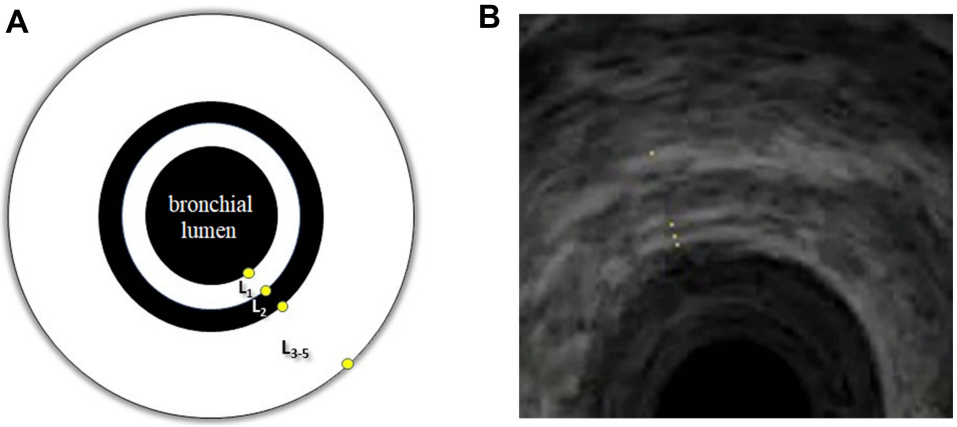

Figure 1 (**A**) Outline of bronchial wall layers. (**B**) Schematic measurement the thicknesses of total bronchial wall and its particular layers in EBUS in a patient with ACO.

find any publications using EBUS to measure the thicknesses of the total bronchial walls and their particular layers in ACO.

In patients with ACO, the thicknesses of the L_1 and L_2 layers were significantly greater than in patients with COPD and significantly smaller than in patients with severe asthma. The total thickness of the bronchial walls and the thickness of the $L_{3–5}$ layers were smaller in ACO and COPD subjects compared to asthma subjects. These results are in line with a previous study conducted in our center where the total thickness of the bronchial walls was significantly greater in patients with severe asthma than in patients with COPD.[17] Moreover, in previous studies by Soja et al,[15,17] patients with asthma and COPD were characterized by significantly greater thicknesses of the bronchial walls and their particular layers than healthy controls. However, Górska et al[18] found no significant differences in the thickness of the bronchial walls measured in EBUS between patients with asthma and COPD. It is believed that as the severity of asthma increases, the airway remodeling is more pronounced, which is manifested by the greater thickness of the bronchial walls.[11,22,23] Mentioned differences are probably due to inclusion of patients with severe asthma in the current study and patients with mild-to-moderate asthma in the study by Górska et al,[18] whilst there is an association between the severity of asthma and the degree of the airway remodeling.

All four available studies assessing the consistency of measurements of bronchial wall thickness in EBUS and HRCT in patients with obstructive pulmonary diseases have proven that the total thickness of the bronchial wall measured in EBUS did not differ significantly from measurements obtained in HRCT, which is recognized as the reference method.[14,15,17,18] HRCT allows to measure only the total thickness of the bronchial wall without assessing its particular layers. In a study by Soja et al,[17] the comparison of the EBUS and HRCT measurements in COPD patients did not show significant differences, although the total bronchial wall thickness assessed using EBUS was slightly greater than that assessed with HRCT (1.192 ±0.079 mm vs 1.173 ±0.064 mm, p=0.1). The studies using EBUS to assess the thicknesses of the bronchial wall layers in patients with ACO are lacking; therefore, we were able to interpret our results only in the context of reports in which these measurements were performed with HRCT. In Kitaguchi et al study,[24] the thickness of segmental bronchial walls and emphysema score were measured in patients with ACO, COPD, and asthma with persistent bronchial obstruction. More than half of patients with asthma, every third patient with ACO and every fourth patient with COPD were characterized by the thickening of the bronchial wall; however, statistically significant differences were only demonstrated between the patients with asthma and COPD. The authors of the study showed the results using a semi-quantitative scale as opposed to the quantitative assessment used in the present study. Similarly, in a study by Fayed et al,[25] the bronchial wall thickness measured by HRCT was increased in patients with asthma compared to those with ACO and COPD, but the percentage of bronchial wall thickness (outlined as the ratio of the wall thickness to the external diameter) was lower in ACO subjects than asthma subjects. While, in a study by Niwa et al,[26] patients with ACO were characterized by thicker airway walls at the level of the third-generation bronchi in multidetector row

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Table 2 Comparison of Basic Characteristics Results Between Study Groups

Parameters	Group			*P value*
	ACO (n=17)	COPD (n=17)	Asthma (n=33)	
Age [years], median (IQR)	66 (62–68)	69 (64–79)	55 (47–60)	*p*<0.001 * COPD, ACO>Asthma
Male sex	9 (52.94%)	11 (64.71%)	11 (33.33%)	*p*=0.088
BMI [kg/m^2], median (IQR)	27.12 (25.31–29.76)	26.45 (24.22–31.74)	26.03 (24.49–29.34)	*p*=0.664
Duration of the disease [years], median (IQR)	16.5 (8.75–36.0)	7.0 (4.75–12.25)	13.0 (7.75–23.5)	*p*=0.052
Diagnosis of the disease before 40 years of age	7 (41.18%) **	0 (0.00%)	18 (54.55%) **	*p*=0.001 * Asthma, ACO>COPD
Smoking [pack-years], median (IQR)	30 (20–40)	30 (20–40)	0 (0–0)	*p*<0.001 * ACO, COPD>Asthma
Mild to moderate exacerbations in last 12 months [number], median (IQR)	2 (0–4)	1 (0–1)	2 (1–3)	*p*=0.009 * Asthma>COPD
Severe exacerbations in last 12 months [number], median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	*p*=0.784
All exacerbations in last 12 months [number], median (IQR)	3 (1–4)	2 (0–3)	4 (1–7)	*p*=0.078
GOLD groups				
A	0 (0%)	2 (11.76%)	–	–
B	6 (35.29%)	5 (29.41%)	–	*p*=1,0
C	1 (5.88%)	0 (0%)	–	–
D	10 (58.82%)	10 (58.82%)	–	*p*=1,0
ACT [points], median (IQR)	17 (11–19)	–	13.5 (9–17.5)	*p*=0.522
CAT [points], median (IQR)	21 (18.25–26.75)	18 (13.5–23)	–	*p*=0.274
mMRC [points], median (IQR)	3 (2–3)	3 (2–3)	–	*p*=0.981

Notes: Data is presented as median (IQR) for continuous variables and count (%) for categorical variables. *Statistically significant (p<0,05). **Missing data for 1 patient.
Abbreviations: BMI, body mass index; ACT, Asthma Control Test; CAT, COPD Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified Medical Research Council Dyspnea Scale.

computed tomography than patients with asthma. We only included patients with severe asthma in our study and it is well known that as the severity of asthma increases, the remodeling of the airways is also more pronounced, which could explain the contradictory results. In the studies by Hardin et al[27] and Suzuki et al,[28] ACO subjects had thicker airway walls expressed as bronchial surface areas in HRCT compared to COPD subjects. However, this technique does not allow to assess the thicknesses of the bronchial layers, but only the thicknesses of the total bronchial walls. Moreover, this technique involves a radiation exposure, therefore is not applicable for repeated measurements. It is recognized that in patients with COPD, structural changes most often affect the pulmonary parenchyma in the form of emphysema, and small bronchi and bronchioles, unlike in patients with asthma, in whom the larger, more proximal airways are most affected. Probably both processes occur in the ACO. In our study, we only evaluated segmental bronchi, without assessing small bronchi and bronchioles or the degree of emphysema. According to Postma et al study,[29] remodeling should be assessed taking into account specific pulmonary compartments such as large airways, small airways, alveoli and lung parenchyma. However, Nakano et al[30] showed

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Table 3 Comparison of Treatment, Laboratory and Spirometry Results Between Groups

Parameters	Group			*P value*
	ACO (n=17)	COPD (n=17)	Asthma (n=33)	
OCSs	3 (17.65%)	2 (11.76%)	18 (54.55%)	*p*=0.003 * Asthma>COPD
ICSs	17 (100.00%)	7 (41.18%)	33 (100.00%)	*p*<0.001 * ACO, Asthma>COPD
ICSs dose (fluticasone propionate) [μg], median (IQR)	400 (320–1400)	400 (360–860)	1000 (800–1920)	*p*=0.01 * Asthma>ACO, COPD
LABAs	17 (100.00%)	15 (88.24%)	33 (100.00%)	*p*=0.123
LAMAs	12 (70.59%)	14 (82.35%)	8 (24.24%)	*p*<0.001 * COPD, ACO>Asthma
A history of atopy	5 (29.41%)	0 (0.00%)	15 (45.45%) **	*p*=0.003 * Asthma, ACO>COPD
Total IgE ≥ 100 IU/mL	8 (47.06%)	2 (11.76%)	18 (54.55%)	*p*=0.013 * Asthma, ACO>COPD
Absolute eosinophil count [cells/μL], median (IQR)	170 (60–580)	200 (130–320)	190 (100–380)	*p*=0.995
Percentage of eosinophils in blood [%], median (IQR)	1.8 (0.9–7.5)	2.6 (1.2–4.15)	3.5 (1.4–5.2)	*p*=0.85
FEV_1/FVC [%], median (IQR)	57.7 (53.07–61.24)	47.08 (42.84–56.92)	64.12 (55.14–73.2)	*p*<0.001 * Asthma>ACO, COPD
FEV_1 [l], median (IQR)	1.48 (1.16–2.04)	1.03 (0.85–1.12)	1.98 (1.48–2.25)	*p*<0.001 * Asthma, ACO> COPD
FEV_1 [%],median (IQR)	62.1 (50.95–74.45)	44.7 (33.6–53.07)	68 (54.2–79.45)	*p*=0.002 * Asthma, ACO> COPD
FEV_1/FVC [%] after SABA, median (IQR)	59.28 (57.42–61.13)	51.52 (44.88–58.28)	68.62 (62.29–76.24)	*p*<0.001 * Asthma>ACO, COPD
FEV_1 after SABA [l], median (IQR)	1.71 (1.46–2.13)	1.13 (1.02–1.51)	2.17 (1.8–2.69)	*p*<0.001 * Asthma, ACO> COPD
FEV_1 after SABA [%], median (IQR)	68.34 (57–78.7)	51 (35–57.6)	80.7 (55.7–92)	*p*=0.01 * Asthma, ACO> COPD

Notes: Data is presented as median (IQR) for continuous variables and count (%) for categorical variables. *Statistically significant (p<0,05). **Missing data for 1 patient.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OCSs, oral corticosteroids; ICSs, inhaled corticosteroids; LABAs, long-acting β_2-agonists; LAMAs, long-acting muscarinic antagonists; IgE, immunoglobulin E; SABA, short-acting β_2-agonist.

that in COPD patients bronchial wall thickening observed in CT closely correlates with small airway dimensions in histological specimens and thus may indirectly indicate small airway disease. In Hardin et al study,[27] which enrolled more than 3000 COPD patients, ACO subjects were characterized by less severe emphysema, more advanced airway disease expressed as the size of the surface area of the segmental and subsegmental bronchial wall, and no significant difference in air trap compared to patients with COPD.

In ACO patients, the thicknesses of total bronchial wall and layers corresponding to cartilage correlated negatively with MEF50% and MEF25%, which are representative for flow in the small airways. The thickness of bronchial walls and their particular layers in EBUS did not correlate with FEV_1 obtained in spirometry in patients with ACO.

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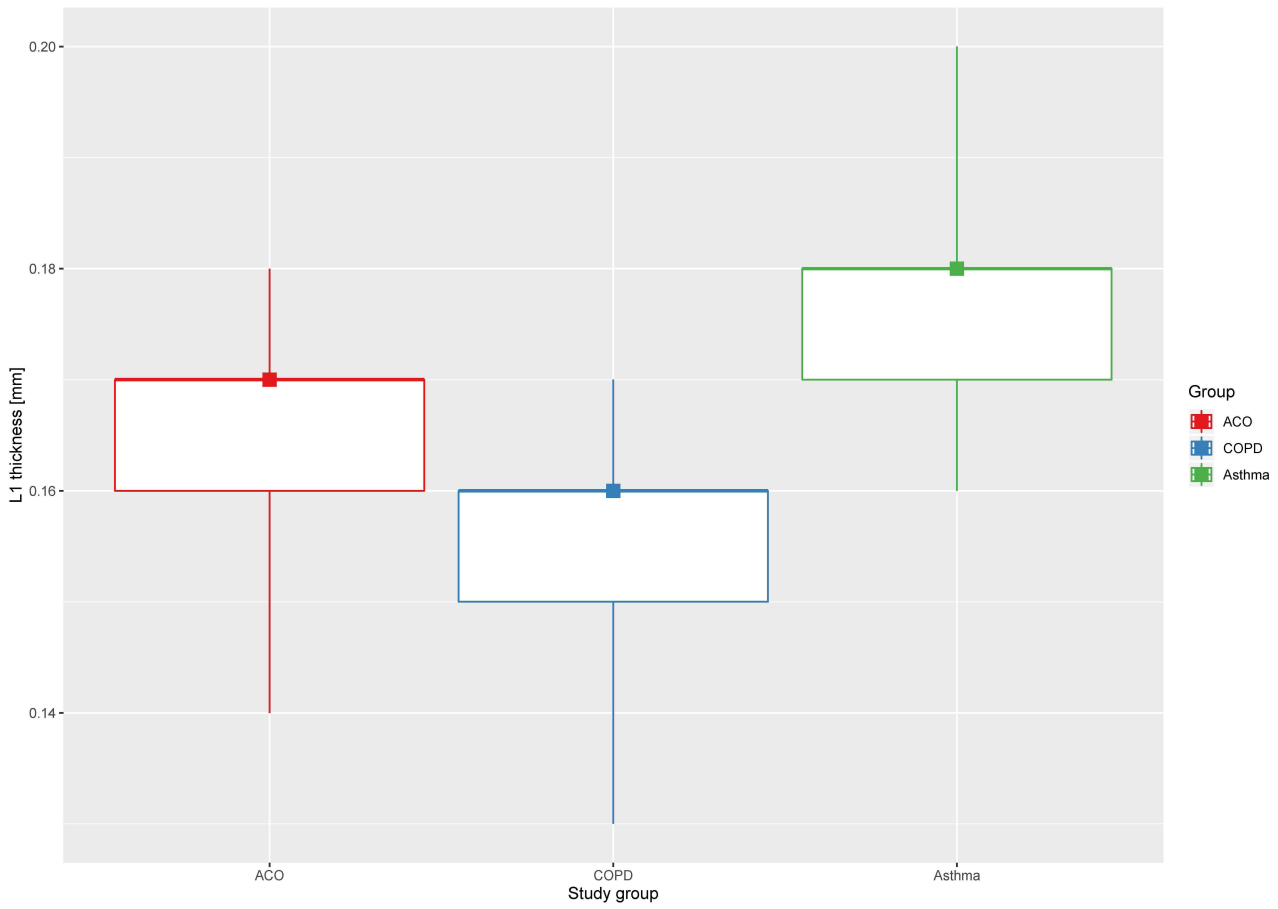

Figure 2 Comparison of the thickness of L_1 [mm, median (IQR)] in patients with ACO, COPD and severe asthma (p<0.001).

Similarly, there was no correlation between FEV_1 with neither the thicknesses of the total bronchial walls nor the thicknesses of their individual layers in COPD subjects. In Soja et al study,[15] a negative correlation was shown between the thickness of total bronchial wall and FEV_1 in patients with asthma, which was confirmed in the current study. In the study by Górska et al,[18] no correlation was found between the thicknesses of the bronchial walls in EBUS and the results obtained from pulmonary function tests in patients with COPD and mild-to-moderate asthma. In a study by Nakano et al,[11] there were COPD subjects with similar degrees of airflow limitation whose abnormalities appeared to be predominantly related to airway remodeling or whose abnormalities appeared to be predominantly related to a loss of lung parenchyma. Although remodeling influences the thicknesses of the total bronchial walls and their particular layers, the degree of bronchial obstruction in ACO and COPD is dependent on other factors, eg, presence of emphysema, which was not assessed in the current study. Unfortunately, there is lack of studies in the literature comparing the bronchial wall thickness with the duration of the disease, the degree of disease control, the severity of symptoms and the dose of ICSs in patients with ACO, COPD and asthma.

This study has several limitations. First, the sample size was limited due to the necessity to perform bronchoscopy; therefore, some differences between the groups may have been disregarded, because of the insufficient statistical power. Second, the study groups differed in some clinical features due to the natural discrepancies in the population among patients with ACO, COPD and asthma. ACO and COPD subjects were older than those with asthma. COPD patients had a significantly more severe degree of bronchial obstruction compared to ACO and asthma patients. Patients also differed in terms of the ICSs doses and the percentage of OCSs and ICSs users, which could have influenced the outcomes. Third, it is increasingly emphasized that asthma, COPD and probably ACO are not single disease entities but a group of different phenotypes. In the presented study, the diagnosis of ACO was established on the basis of the GINA and GOLD criteria,

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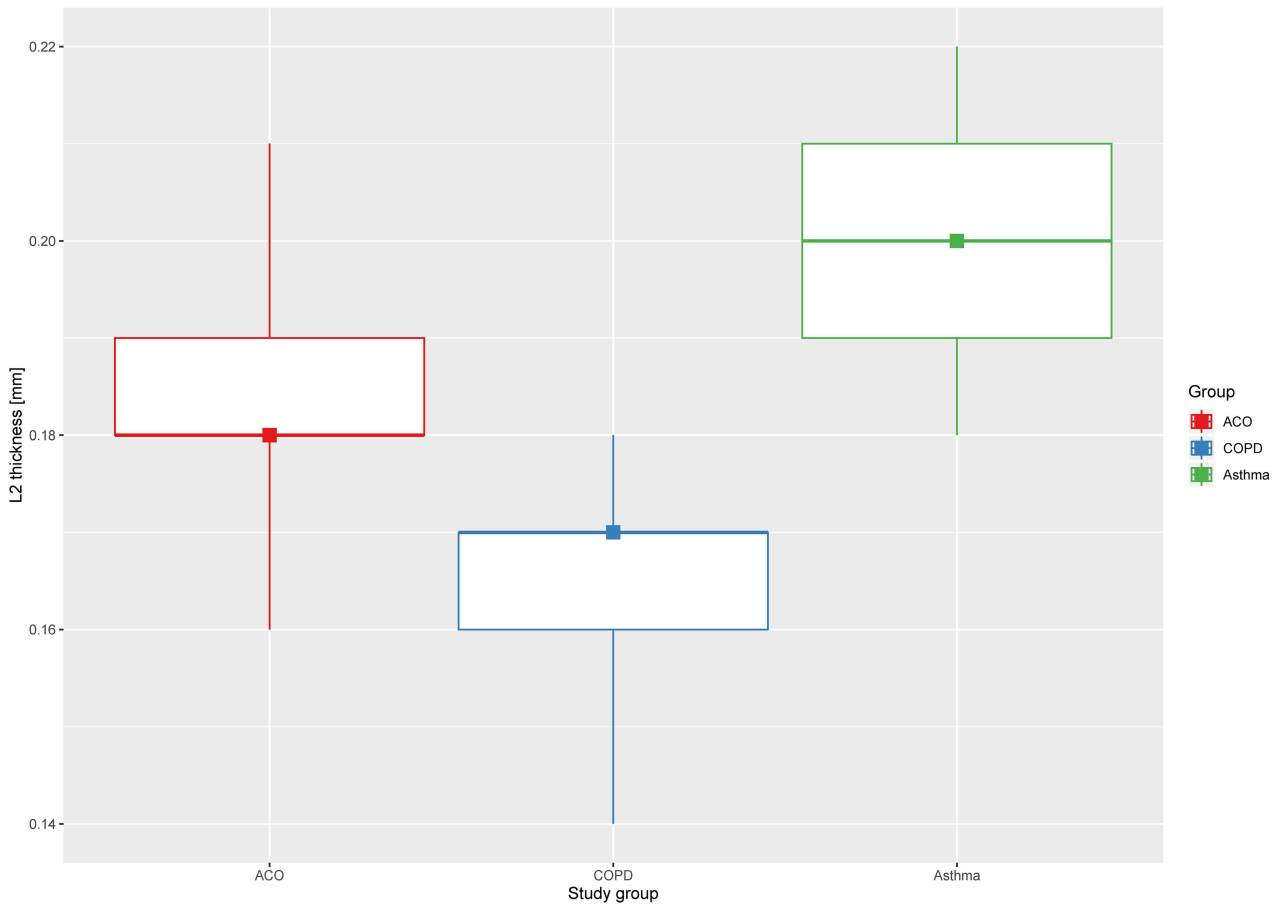

Figure 3 Comparison of the thickness of L_2 [mm, median (IQR)] in patients with ACO, COPD and severe asthma (p<0.001).

which are the least restrictive and are mainly based on medical diagnosis, so the patients included in the study were not a homogeneous group. Based on the available studies, whose main purpose was to evaluate the concordance of the different diagnostic ACO criteria, the level of agreement between different ACO definitions is poor.[2,31] Similarly, due to the small size of the studied groups, patients with COPD and asthma were not analyzed in terms of their different phenotypes. Demonstrating differences between patients who constitute a set of different subgroups is a great challenge. Moreover, we do not know whether the greater thickness of the layers in ACO patients requires different strategy of treatment, such as higher doses of inhaled steroids. It is known from previous studies that as the severity of asthma increases, the remodeling of the airways is also more pronounced, which is manifested by the greater thickness of the bronchial walls.[11] Patients with more severe asthma generally require higher doses of inhaled steroids. It is unknown whether this would also be appropriate in patients with ACO, because airflow limitation in these patients is not only a result of airway remodeling, but it can

Table 4 The Thickness of the Bronchial Walls (L_1 + L_2 + $L_{3–5}$) and Their Individual Layers: L_1, L_2, $L_{3–5}$ Measured by the EBUS Method

Parameters	Group			*P value*
	ACO (n=17)	COPD (n=17)	Asthma (n=33)	
Thickness of L_1 [mm], median (IQR)	0.17 (0.16–0.17)	0.16 (0.15–0.16)	0.18 (0.17–0.18)	p<0.001 * Asthma>ACO>COPD
Thickness of L_2 [mm], median (IQR)	0.18 (0.18–0.19)	0.17 (0.16–0.17)	0.2 (0.19–0.21)	p<0.001 * Asthma>ACO>COPD
Thickness of $L_{3–5}$ [mm], median (IQR)	0.85 (0.83–0.88)	0.81 (0.76–0.88)	0.92 (0.84–0.99)	p=0.001 * Asthma>ACO,COPD
Thickness of L_1+L_2+ $L_{3–5}$ [mm], median (IQR)	1.2 (1.16–1.23)	1.14 (1.07–1.21)	1.31 (1.2–1.38)	p<0.001 * Asthma>ACO,COPD

Notes: Data is presented as median (IQR). L_1- layer 1, L_2- layer 2, $L_{3–5}$- layer 3–5, L_1+L_2+$L_{3–5}$- total bronchial wall, *Statistically significant (p<0.05).

Table 5 Correlation Between the Thickness of Bronchial Layers and Spirometry Parameters, Disease Duration, Disease Control, Severity of the Symptoms and ICS Dose in the ACO Group

Correlation	Thickness of the Layer			
	L_1	L_2	L_{3-5}	$L_1+L_2+L_{3-5}$
FEV_1 [l]	r=0.039, p=0.886	r=−0.225, p=0.402	r=−0.117, p=0.667	r=−0.178, p=0,51
FEV_1 [%]	r=0.339, p=0.199	r=−0.037, p=0.892	r=0.056, p=0.837	r=0.058, p=0.832
FEV_1 after SABA [l]	r=−0.005, p=0.987	r=−0.291, p=0.274	r=−0.062, p=0.82	r=−0.143, p=0.597
FEV_1 after SABA [%]	r=0.304, p=0.236	r=−0.039, p=0.883	r=0.296, p=0.248	r=0.278, p=0.28
MEF75 [%]	r=0.269, p=0.314	r=−0.025, p=0.928	r=−0.213, p=0.429	r=−0.205, p=0.446
MEF50 [%]	r=−0.037, p=0.893	r=−0.109, p=0.687	r=−0.602, p=0.014 *	r=−0.629, p=0.009 *
MEF25 [%]	r=0.003, p=0.991	r=0.002, p=0.995	r=−0.577, p=0.019 *	r=−0.57, p=0.021 *
Duration of the disease [years]	*r*=0.128; *p*=0.636	*r*=−0.17; *p*=0.53	*r*=−0.485; *p*=0.057	*r*=−0.438;. *p*=0.09
ACT [points]	*r*=−0.014; *p*=0.957	*r*=−0.049; *p*=0.851	*r*=−0.185; *p*=0.477	*r*=−0.272; *p*=0.29
CAT [points]	*r*=0.071; *p*=0.809	*r*=0.101; *p*=0.73	*r*=0.206; *p*=0.48	*r*=0.306; *p*=0.287
mMRC [points]	*r*=0.031; p=0.917	*r*=0.342; *p*=0.232	*r*=0.125; *p*=0.669	*r*=0.223; *p*=0.443
ICS dose [μg]	*r*=−0.156; *p*=0.549	*r*=−0.118; *p*=0.653	*r*=−0.004; *p*=0.989	*r*=−0.037; *p*=0.886

Notes: *r* – Spearman`s rank correlation coefficient. *Statistically significant (p<0.05).
Abbreviations: FEV_1, forced expiratory volume in 1 second; MEF, maximal expiratory flow; ACT, Asthma Control Test; CAT, COPD Assessment Test; mMRC, Modified Medical Research Council Dyspnea Scale; ICS, inhaled corticosteroid.

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be related to a loss of lung parenchyma. Therapy for asthma has been gradually improved on clinical practice, while airway remodeling is considered the least affected by current pharmacological and biological treatments.[32] Inhaled corticosteroids can obviously reduce inflammation in asthma patients, whereas its impact on preventing or reversing airway remodeling remains under discussion. Many studies suggest that glucocorticoid cannot or slightly impact airway remodeling.[33,34] Perhaps similar results can be expected in ACO patients, but further research is needed to clarify this problem. Regardless of the definition used, ACO accounts for a significant proportion of all obstructive pulmonary diseases, so developing adequate diagnostic tools and the best therapeutic management is an important concern.

Conclusions

In summary, patients with ACO are characterized by more severe structural changes in the airways assessed by EBUS than those with COPD, and less pronounced than patients with severe asthma. These results suggest that EBUS may provide useful information about differences in airway remodeling between ACO, severe asthma and COPD. Besides the methods used to date, including bronchial biopsies and HRCT, EBUS may become a new technique for evaluating ACO remodeling. In contrast to HRCT, the EBUS enables not only to measure the thicknesses of the total bronchial walls, but also to assess the thicknesses of their individual layers. Moreover, it does not cause exposure to ionizing radiation and is a safe, well-tolerated method, that does not involve serious complications.

Abbreviations

ACO, asthma-COPD overlap; ACT, Asthma Control Test; BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EBUS, endobronchial ultrasound; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRCT, high resolution computed tomography; ICSs, inhaled corticosteroids; IgE, immunoglobulin E; L_1, layer 1; L_2, layer 2; L_{3-5}, layer 3–5; $L_1+L_2+L_{3-5}$, total bronchial wall; LABAs, long-acting β_2-agonists; LAMAs, long-acting muscarinic antagonists; mMRC, Modified Medical Research Council Dyspnea Scale; OCSs, oral corticosteroids; SABA, short-acting β_2-agonist.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Science Centre grant (UMO-2015/19/N/NZ5/00268).

Disclosure

The authors report no conflicts of interest in this work.

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