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Asthma with Irreversible Airway Obstruction in Smokers and Nonsmokers: Links between Airway Inflammation and Structural Changes

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Keywords
Asthma · Incomplete reversibility of airway obstruction · Smoking · Chest CT · Airway inflammation

Abstract
Background: The development of irreversible airway obstruction (IRAO) in asthma is related to lung/airway inflammatory and structural changes whose characteristics are likely influenced by exposure to tobacco smoke. ***Objective:*** To investigate the interplay between airway and lung structural changes, airway inflammation, and smoking exposure in asthmatics with IRAO. ***Methods:*** We studied asthmatics with IRAO who were further classified according to their smoking history, those with ≥20 pack-years of tobacco exposure (asthmatics with smoking-related IRAO [AwS-IRAO]) and those with <5 pack-years of tobacco exposure (asthmatics with nonsmoking-related IRAO [AwNS-IRAO]). In addition to recording baseline clinical and lung function features, all patients had a chest computed tomography (CT) from which airway wall thickness was measured and quantitative and qualitative assessment of emphysema was performed. The airway inflammatory profile was documented from differential inflammatory cell counts on induced sputum. ***Results:*** Ninety patients were recruited (57 AwS-IRAO and 33 AwNS-IRAO). There were no statistically significant differences in the extent of emphysema and gas trapping between groups on quantitative chest CT analysis, although Pi10, a marker of airway wall thickness, was significantly higher in AwS-IRAO ($p = 0.0242$). Visual analysis showed a higher prevalence of emphysema ($p = 0.0001$) and higher emphysema score ($p < 0.0001$) in AwS-IRAO compared to AwNS-IRAO and distribution of emphysema was different between groups. Correlations between radiological features and lung function were stronger in AwS-IRAO. In a subgroup analysis, we found a correlation between airway neutrophilia and emphysematous features in AwS-IRAO and between eosinophilia and both airway wall thickness and emphysematous changes in AwNS-IRAO. ***Conclusions:*** Although bronchial structural changes were relatively similar in smoking and nonsmoking patients with asthma and IRAO, emphysematous changes were more predominant in smokers. However, neutrophils in AwS-IRAO and eosinophils in AwNS-IRAO were associated with lung and airway structural changes.

Introduction

Asthma is characterized by variable airway obstruction [1]. However, a component of irreversible airway obstruction (IRAO) may be observed in asthma despite op-

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timal treatment, as universally observed in chronic obstructive pulmonary disease (COPD) [2–5]. Patients sharing features of both asthma and COPD have been labelled as asthma-COPD overlap (ACO) in the past few years, and there has been increasing interest in better characterizing this entity [6]. However, although the Global Initiative for Asthma (GINA) and the Global Obstructive Lung Disease (GOLD) previously published a consensus-based document on ACO [7], the use of this term is debated [8–10], mostly because there is no consensus definition. Hence, the most recent GOLD guidelines have deleted this label [11]. Nevertheless, questions still remain about the characteristics of asthmatic subjects showing IRAO, mostly regarding the differences between those with a significant tobacco smoking history and those who never smoked.

As studies have demonstrated the negative impact of cigarette smoking on asthma-related outcomes [12–15], lung function [16–18], inflammatory [17–19], and structural features [19] in patients with asthma irrespective of airflow limitation, there is a need to better document the impact of smoking in this disease. Hence, we recently reported that smoking asthmatics with IRAO had a more severe asthma phenotype compared to their nonsmoking counterpart [20, 21]. Whether these differences may be related to alterations in the airway or lung structure and to the nature of the airway inflammatory process is uncertain. Indeed, the neutrophil is considered a key cell in the pathogenesis of COPD, particularly in regard to tissue injury and remodeling while eosinophils have been involved in the development of a fixed component of airway obstruction in asthma [22, 23].

In patients with asthma without airflow limitation, we and others reported a higher prevalence of airway and parenchymal abnormalities in smokers than nonsmokers [17, 24]. In patients with asthma and a fixed component of airway obstruction, regardless of smoking history, emphysema has been observed on chest computed tomography (CT), although to a lower extent than in patients with COPD [25, 26]. Furthermore, signs of mild emphysema in nonsmoking patients with asthma and IRAO have been observed in pilot studies including few patients [27, 28] or in subjects who died from asthma [27]. Finally, smokers with asthma and airflow limitation have been shown to present more emphysema as compared to their nonsmoking counterpart [25, 29]. However, these reported results were only based on visual scoring of CT scans.

The main goal of this study was to compare the chest CT features between smoking and nonsmoking asthmatic patients with IRAO by providing a quantitative and qualitative assessment of lung structures in these individuals. We also studied to which extent the radiological abnormalities relate to pulmonary function characteristics in these individuals. Finally, we looked at airway inflammatory phenotypes in both groups and their relationship with lung function and structural changes. Our hypothesis was that smoking would be mostly associated with an emphysematous pattern on chest CT, related to the development of an airway neutrophilia, while in nonsmoking asthmatics, eosinophils would be involved in both bronchial wall thickening and parenchymal changes.

Methods

Participants

A subgroup of a larger cohort participating in an already published study aiming at phenotyping smoking and nonsmoking subjects with IRAO, had CT scans with image analyses. Results from the cross-sectional evaluation and of a 12-month longitudinal comparison of the larger cohort have already been published [20, 21]. Briefly, 2 groups of asthmatic subjects with an IRAO (see inclusion criteria below) were recruited between April 2014 and December 2016 from the asthma outpatient clinic of the *Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval (IUCPQ-UL)*, a tertiary care center in Quebec city: (1) 1 group with a significant smoking history which was labelled asthmatics with smoking-related IRAO (AwS-IRAO) [7] and (2) 1 group without a significant smoking history which was labelled as asthmatics with nonsmoking-related IRAO (AwNS-IRAO) [20]. AwS-IRAO were current or ex-smokers with a ≥20 pack-years history of cigarette smoking, with both features of asthma and COPD, as defined by the GINA report [7]. Current smokers were asked to refrain from smoking for at least 12 h before study visit. The AwNS-IRAO group included never smokers or ex-smokers with <5 pack-years smoking history, who had quitted smoking ≥12 months before inclusion in the study.

To be included in the study, subjects had to (a) be aged ≥45 years; (b) have evidences of airway obstruction variability as shown by either a positive response to bronchodilator (BD) (>200 mL and >12% increase from baseline forced expiratory volume in 1 s [FEV_1]) and/or a positive methacholine bronchoprovocation test (<16 mg/mL) associated with a history of respiratory symptoms [1]; (c) require treatment with inhaled corticosteroids (ICS) with or without additional asthma medication; and (d) show IRAO, as defined by persistence of a post-BD FEV_1/forced vital capacity (FEV_1/FVC) ratio <0.7 in addition to a FEV_1 <80% of predicted value on at least 2 occasions while on optimal asthma treatment according to a respirologist [1]. Subjects were excluded if they had (a) any other respiratory conditions than asthma (including a previous diagnosis of COPD without a confirmed diagnosis of asthma); (b) unstable respiratory or nonrespiratory condition; (c) previous bronchial thermoplasty; (d) evidences of respiratory infection in the 4 weeks preceding study entry; and (e) changes in respiratory medications in the previous 4 weeks. Severity of asthma was defined according to current guidelines [1] as determined by the medication prescribed to keep asthma under control. Asth-

ma was considered as mild if the patient used low doses of ICS (≤250 mcg/day beclomethasone diproprionate [BDP] or equivalent), moderate if the patient used medium doses of ICS (>250 and ≤500 mcg/day BDP or equivalent) alone or mild-to-moderate dose of ICS in combination with additional therapy (long-acting beta-agonist [LABA] or leukotriene receptor antagonist), and severe if the patient used high doses of ICS (>500 mcg/day BDP or equivalent) and additional pharmacotherapy (LABA, leukotriene receptor antagonist, and/or oral corticosteroids). All subjects signed an informed consent form and the study was approved by the Ethics Committee of the IUCPQ-UL (CÉR 21047).

Study Design

This was a cross-sectional study comparing clinical characteristics, expiratory flows, lung volumes, carbon monoxide diffusion capacity (D_LCO), airway inflammation from induced sputum analysis, and chest CT features between the 2 groups of interest.

Evaluation

Extensive clinical characterization, including atopic status using allergy skin-prick tests, assessment of asthma control with the validated French version of the Asthma Control Questionnaire (ACQ) [30], and recording of asthma exacerbations as defined according to the American Thoracic Society/European Respiratory Society (ATS/ERS) statement [31] was performed.

Baseline FEV_1 and FVC were measured according to the ATS criteria [32]. Predicted values were obtained from the ERS Global Lung Function Initiative (GLI-2012) [33, 34]. Reversibility of airway obstruction was measured after administration of 200–400 mcg of inhaled salbutamol. Lung volumes and D_LCO were measured as per ATS/ERS standards [35, 36]. Before pulmonary function tests, short-acting β2-agonists and short-acting muscarinic-antagonists, LABA and long-acting muscarinic antagonists were withheld at least 8, 12, and 24 h, respectively.

Airway Inflammation

Sputum was induced by inhalation of hypertonic saline and processed using the method described by Pin et al. [37] and modified by Pizzichini et al. [38]. Total cell count was determined using a Neubauer hemacytometer chamber. A differential cell count, including eosinophils, neutrophils, macrophages, lymphocytes, and bronchial cells was performed by an experienced technician. Airway inflammation was categorized into inflammatory phenotypes as follows: eosinophilic (eosinophils ≥3% and neutrophils <64.4%), neutrophilic (eosinophils <3% and neutrophils ≥64.4%), mixed (eosinophils ≥3% and neutrophils ≥64.4%), and paucigranulocytic (eosinophils <3% and neutrophils <64.4%) [39, 40].

CT Image Acquisition

CT images were acquired using either a Siemens SOMATOM Definition or a Philips iCT 256 scanner with the subject supine at suspended full inspiration and full expiration from apex to base of the lung. The CT parameters for image acquisition were as follows: 120 kVp, 100 mA, 0.5 s gantry rotation, 1.0 mm slice thickness, and an intermediate reconstruction kernel (Siemens: B35; Philips: B).

CT Image Analysis

CT images were analyzed using the Apollo 2.0 software package (VIDA Diagnostics Inc., Corralville, IA, USA). Briefly, emphysema was defined as the percent of CT voxels < −950 HU (%LAA950) on full-inspiration CT [41] and gas trapping was defined as the percent of CT voxels < −856 HU (%LAA856) using the full-expiration CT images [41]. The airway tree was segmented using the automatic segmentation tool with manual intervention to verify the segmentation results. Airway inner lumen area, lumen diameter, and airway wall area were generated for all segmental, subsegmental, and sub-sub-segmental airways. A measurement of airway wall thickness, Pi10, was calculated for a theoretical airway with an internal perimeter of 10 mm using the regression equation for the square root of wall area versus internal perimeter for all measured airways as previously described [42].

We used the CanCOLD scoring system as described by Tan et al. [43] for qualitative assessment of the extent and distribution of emphysema as well as gas trapping and airway wall thickness. Briefly, emphysema was scored using a five-point scale (0 = no emphysema, 1 = 1–25% [trivial], 2 = 26–50% [mild], 3 = 51–75% [moderate], 4 = 76–100% [severe-very severe]) for 6 lung zones (upper left and upper right above the carina; mid [middle left and middle right] between carina and inferior pulmonary veins; and lower [lower left and lower right] zones). The presence of emphysema was summed across all zones for all scores ≥1. Presence of expiratory air trapping, bronchial wall thickening, and bronchiectasis were assessed based on morphological criteria from the Fleishner glossary of terms for thoracic imaging [44].

Statistical Analysis

Nominal variables were expressed in percentage (%) and were analyzed using Fisher's exact test. Continuous variables expressed with mean ± SD were analyzed using one-way ANOVA to compare groups. Statistical model with heterogeneous variances was tested whether the model could be reduced to a one-way analysis with the same variance between groups. When effect that specifies heterogeneity in the covariance structure was significant (heteroscedasticity) compared to the same variance between groups, the statistical analysis was performed using separate residual variance per group. Satterthwaite's degree of freedom statement was added for unequal variance structures. The normality assumption was verified with the Shapiro-Wilk tests, after a Cholesky factorization on residuals from the statistical model. Brown and Forsythe's variation of Levene's test statistic was used to verify the homogeneity of variances. Continuous variables expressed with median and interquartile range were analyzed using one-way ANOVA on ranks. All statistical analyses were adjusted for differences in female sex proportion as well as age, BMI, and duration of disease. Correlations between variables were expressed using Spearman's correlation coefficients. The results were considered significant with p values ≤0.05. All analyses were conducted using the statistical package SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (R Core Team [2018], Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 224 consecutive subjects with asthma were screened for inclusion/exclusion criteria, of which 90 with IRAO were included in the analysis, 57 in the AwS-IRAO group and 33 in the AwNS-IRAO group (Fig. 1).

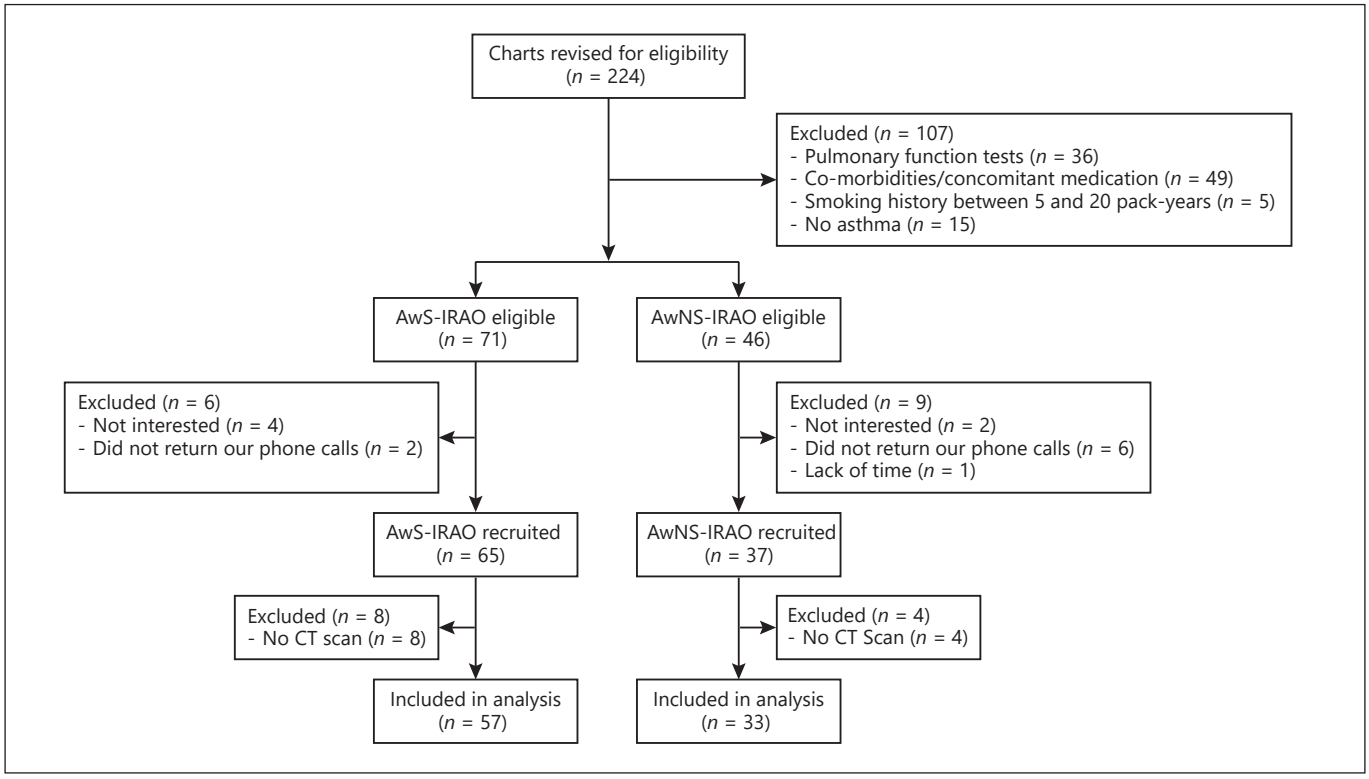

Fig. 1. Flowchart of study participants. IRAO, irreversible airway obstruction; AwS-IRAO, asthmatics with smoking IRAO; AwNS-IRAO, asthmatics with nonsmoking IRAO; CT, computed tomography.

Subjects' Characteristics

Table 1 shows subjects' demographics. The AwS-IRAO group included 45 ex-smokers and 12 current smokers. The proportion of women was greater in the AwS-IRAO group compared to the AwNS-IRAO group. Daily dose of ICS was similar between groups, but the proportion of subjects in the AwS-IRAO group that was taking a long-acting muscarinic-antagonist was greater than that in the AwNS-IRAO group. None of the subjects were taking anti-IgE medication or prednisone. In addition, asthma control score was significantly higher in AwS-IRAO. No between-group differences were seen for the number of unscheduled medical visits, emergency room visits, and hospitalizations in the year preceding the study. Sub-analyses comparing current versus ex-smokers within the AwS-IRAO group and ex-smokers in the AwS-IRAO group versus the AwNS-IRAO group are presented in online suppl. Tables 1, 2 (for all online suppl. material see www.karger.com/doi/10.1159/000508163).

Pulmonary Function

Post-BD FEV_1 tended to be lower, and residual volume was significantly higher in AwS-IRAO subjects compared to their AwNS-IRAO counterparts (Table 2). In addition, AwS-IRAO subjects had a significantly lower D_LCO and KCO compared to AwNS-IRAO.

Airway Inflammation

Good-quality sputum samples were obtained in 33 AwS-IRAO subjects and in 19 AwNS-IRAO subjects. Overall, the airway inflammatory profile was similar in AwS-IRAO and AwNS-IRAO (Table 1). However, the proportion of subjects with an eosinophilic profile was numerically greater in AwNS-IRAO (47%) compared to AwS-IRAO (24%). In AwS-IRAO, the airway inflammatory profile showed a paucigranulocytic, eosinophilic, neutrophilic, and mixed profile in 42, 24, 21, and 9% of the subjects, respectively.

Radiological Features

Using quantitative CT, the extent of emphysema and gas trapping was not statistically different between the 2

Table 1. Subjects' demographics

	AwNS-IRAO	AwS-IRAO	*p* value
Subjects, *n*	33	57	
Women/men	13/20	39/18	**0.0087**
Age, years, mean±SD (range)	63±9 (44–76)	60±10 (44–84)	0.2805
BMI, kg/m^2	28±5	29±6	0.4256
Smoking history			
Never smokers	23 (70)	0	
Ex-smokers	10 (30)†	45 (79)	
Current smokers	0	12 (21)	
Pack-years	3±2	35±14	**<0.0001**
Asthma duration, years	33±21	24±18	**0.0378**
Asthma severity			
Mild	1 (3)	1 (2)	0.7703
Moderate	15 (45)	30 (53)	
Severe	17 (52)	26 (46)	
Dose of ICS, mcg/day (equivalent beclomethasone), median (interquartile range)	600 (500, 1,000)	500 (500, 1,000)	0.4376
ICS + LABA	29 (88)	53 (93)	0.4581
LABA	4 (12)	2 (4)	0.1867
LTRA	9 (27)	10 (18)	0.2952
LAMA	5 (15)	31 (54)	**0.0003**
SAMA	0	1 (2)	1.000
SABA*	5 (15)	7 (12)	0.7531
Asthma control score, mean (range)	0.9 (0–3.7)	1.3 (0.2–4.0)	**0.0183**
Acute care use in the previous year (total number of events)			
Unscheduled medical visits related to respiratory problems	9 (0.3±0.6)	18 (0.3±0.7)	
Emergency room visits (<24 h)	6 (0.2±0.5)	27 (0.5±1.2)	
Hospitalizations (>24 h)	1 (0±0.2)	6 (0.1±0.4)	
Health care use, total number of events (mean number of events/subject±SD)			
Oral corticosteroids in the previous year	12 (0.4±0.6)	44 (0.8±1.2)	
Atopy (yes)	26 (79)	41 (72)	0.6042
Sputum TCC, median (interquartile range)**	6.1 (4.2, 2.3)	8.6 (7.0, 13.0)	0.5166
Sputum neutrophils, %, median (interquartile range)**	48.5 (29.5, 78.0)	44.3 (33.0, 65.0)	0.9254
Sputum eosinophils, %, median (interquartile range)**	4.0 (0.8, 22.5)	1.5 (0.5, 5.3)	0.1788
Sputum inflammatory phenotype**			
Eosinophilic	9 (47)	8 (24)	0.1920
Neutrophilic	5 (26)	7 (21)	
Mixed	2 (11)	3 (9)	
Paucigranulocytic	3 (16)	14 (42)	
Blood eosinophils, ×10^9/L, median (interquartile range)	0.148 (0.10, 0.39)	0.17 (0.10, 0.30)	0.4220

Results are presented as mean±SD for continuous variables or as number (%) of patients for categorical variables, unless stated otherwise. Statistically significant *p* values appear in bold. AwNS-IRAO, asthmatics with nonsmoking incomplete reversibility of airway obstruction; AwS-IRAO, asthmatics with smoking IRAO; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic-agonist; SD, standard deviation. * Patients not having a SABA as rescue medication were using their combined ICS-LABA as rescue medication. ** Sputum samples were obtained in 19 subjects with AwNS-IRAO and in 33 subjects with AwS-IRAO. † Ex-smokers in the AwNS-IRAO group all had a cumulative tobacco exposure <5 pack-year.

groups (Table 3). However, the CT measured airway wall thickness (Pi10) was greater in the AwS-IRAO group. Qualitative CT scan evaluations are also presented in Table 3. AwS-IRAO subjects had a greater prevalence of emphysema and a higher emphysema score as assessed by a radiologist compared to AwNS-IRAO individuals. In addition, the distribution of emphysema was different between the 2 groups, the AwS-IRAO group showing mostly a mixed centrilobular and distal acinar or paraseptal pattern, whereas most AwNS-IRAO subjects exhibited

Table 2. Pulmonary function

	AwNS-IRAO	AwS-IRAO	*p* value
Number of subjects	33	57	
Spirometry			
Pre-BD FEV_1, % (predicted)	61±12	57±13	0.1976
Pre-BD FVC, % (predicted)	81±12	80±13	0.6740
Pre-BD FEV_1/FVC	0.58±0.06	0.56±0.08	0.2157
Post-BD FEV_1, % (predicted)	67±15	60±15	0.0644
Post-BD FVC, % (predicted)	86±13	84±15	0.5025
Post-BD FEV_1/FVC	0.59±0.08	0.57±0.10	0.1777
Reversibility to BD, %	12±11	13±11	0.5752
Lung volumes			
TLC, % (predicted)	102±12	107±17	0.0653
FRC, % (predicted)	105±20	110±26	0.3991
RV, % (predicted)	122±30	145±48	**0.0076**
ERV	0.74±0.45	0.68±0.43	0.5313
D_LCO, % (predicted)	88±24	77±20	**0.0297**
KCO, % (predicted)	106±22	91±22	**0.0024**

Results are presented as mean±SD. Statistically significant *p* values appear in bold. AwNS-IRAO, asthmatics with nonsmoking incomplete reversibility of airway obstruction; AwS-IRAO, asthmatics with smoking IRAO; BD, bronchodilator; D_LCO, single-breath diffusing capacity for carbon monoxide; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; KCO, diffusing capacity for carbon monoxide corrected for alveolar volume; RV, residual volume; TLC, total lung capacity.

centrilobular emphysema. The prevalence of bronchial wall thickening, air trapping, and bronchiectasis was similar between groups.

Correlations between Clinical and Radiological Features

Correlations between chest CT measurements and lung function or volumes are shown in Table 4. Pi10 showed significant correlations with post-BD FEV_1 percent predicted and FEV_1/FVC only in AwS-IRAO. In addition, in patients with AwS-IRAO, both %LAA950 and visual emphysema score significantly correlated with post-BD FEV_1/FVC and lung volume parameters as well as with D_LCO, although this was not observed in patients with AwNS-IRAO. Only %LAA856 was significantly correlated with post-BD FEV_1/FVC and with lung volumes in both groups.

Airway Inflammation and Structural Airway/Lung Change

There was a significant correlation between absolute number of neutrophils in sputum and % emphysema for all subjects ($r_s = 0.312$, $p = 0.02$) and between both absolute number and % neutrophils in sputum and % emphysema in AwS-IRAO patients ($r_s = 0.467$, $p = 0.006$ and $r_s = 0.385$, $p = 0.03$, respectively) but not in AwNS-IRAO. In contrast, in AwNS-IRAO subjects, there was a correlation between absolute number of eosinophils in sputum and airway wall thickness (Pi10) ($r_s = 0.484$, $p = 0.04$) and emphysema score ($r_s = 0.541$, $p = 0.02$).

Discussion

This study is unique in comparing quantitative and qualitative chest CT assessment of lung structure in well characterized smoking and nonsmoking asthmatics with a component of IRAO and in exploring the relationship between chest CT changes and both inflammatory and physiological features. Our results showed that there were several similarities in quantitative chest CT features, although qualitative CT revealed radiological differences between the 2 groups. Of interest, we observed that airway wall thickness and emphysema correlated with airway obstruction only in AwS-IRAO whereas air trapping and airway obstruction correlated in both groups. Finally, this study is the first to suggest a role of neutrophils in structural lung changes in AwS-IRAO while airway eosinophils correlated with both airway and parenchymal changes in AwNS-IRAO.

Our data indicate that AwS-IRAO and AwNS-IRAO subjects had, on quantitative chest CT analysis, similar percentages of emphysema and gas trapping, as well as similar inspiratory and expiratory total volume and inner lumen area. Furthermore, smokers presented thicker airway walls as compared to nonsmokers, although this difference was very small. Thomson and colleagues also reported similar percentages of emphysema between smokers and nonsmokers with asthma, although their study included a more heterogeneous population of asthmatic patients with and without IRAO [24]. Our study is also more comprehensive in reporting data related to gas trapping, lung volumes, airway wall thickness, and lumen area in 2 subpopulations of well-defined asthmatics with IRAO.

Using qualitative assessment of CT features, we observed a significantly higher prevalence of emphysema and a higher emphysema score in AwS-IRAO as compared to AwNS-IRAO, although both scores were associated to trivial emphysema, in keeping with other observations [25, 29]. We also observed a different distribution of emphysematous changes between groups, AwNS-IRAO presenting a more centrilobular distribution and AwS-IRAO having a more panlobular and paraseptal pattern.

Table 3. CT features

	AwNS-IRAO	AwS-IRAO	*p* value	Adjusted *p* value
Number of subjects	33	57		
Quantitative features				
Emphysema, %LAA950, median (interquartile range)	6.1 (3.4, 9.4)	5.0 (2.9, 9.8)	0.7345	0.5429
Air trapping, %LAA856, median (interquartile range)	41.16 (18.90, 70.90)	27.01 (6.78, 73.21)	0.1054	0.4499
TLVins, mL	5.417±1.429	5.335±1.178	0.7729	0.1984
TLVexp, mL	3.914±1.188	3.784±1.148	0.6534	0.3737
Airway wall thickness, Pi10, mm	4.1±0.2	4.2±0.2	0.2769	**0.0242**
Inner lumen area, median (interquartile range)	13.2 (11.6, 14.8)	12.58 (6.22, 23.61)	0.5269	0.5341
Qualitative features				
Emphysema score	1.1±2.7	5.3±6.1	**0.0003**	**<0.0001**
Emphysema*	6 (19)	35 (61)	**0.0001**	
Type of emphysema, *n* (% of patients with emphysema)				
Bulla	1 (17)	3 (9)	**0.0034**	
Centrilobular	4 (67)	10 (29)		
Distal acinar or paraseptal	1 (17)	2 (6)		
Panlobular	0	2 (6)		
Mixed centrilobular and distal acinar or paraseptal	0	18 (51)		
Bronchiolitis	20/32 (63)	22/55 (40)	0.3738	
Bronchial wall thickening	26/32 (81)	45/55 (82)	1.0000	
Bronchiectasis	2/32 (6)	2/55 (4)	0.6228	
Expiratory air trapping	13/32 (41)	17/55 (31)	0.4833	

Results are presented as mean±SD for continuous variables or as number (%) of subjects for categorical variables, unless stated otherwise. Adjusted *p*: analyses were adjusted for differences in female sex proportion, age, BMI, and duration of disease. Statistically significant *p* values appear in bold. CT, computed tomography; %LAA950, the percentage of lung voxels with a CT attenuation value < −950 HU on an inspiratory CT scan, represents the percentage of emphysema in the lung; %LAA856, the percentage of lung voxels with a CT attenuation value < −856 HU on an expiratory CT scan, represents the percentage of gas trapping in the lung; AwNS-IRAO, asthmatics with nonsmoking incomplete reversibility of airway obstruction; AwS-IRAO, asthmatics with smoking IRAO; TLVin, inspiratory total lung volume; TLVex, expiratory total lung volume. * The presence of emphysema was a summation emphysema score ≥1, as determined by adding the extent of emphysema scored on a 5-point scale (0 = no emphysema, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100%) among 6 lung zones (upper left and upper right above the carina; mid [middle left and middle right] between carina and inferior pulmonary veins; and lower [lower left and lower right] zones).

Table 4. Correlations between CT features and lung function and volumes

	AwNS-IRAO				AwS-IRAO			
	airway wall thickness, Pi10, mm	emphysema, %LAA950	air trapping, %LAA856	visual emphysema score	airway wall thickness, Pi10, mm	emphysema, %LAA950	air trapping, %LAA856	visual emphysema score
Post-BD FEV_1, % (predicted)	−0.055	−0.114	−0.098	−0.124	**−0.405***	**−0.324***	−0.266	−0.116
Post-BD FEV_1/FVC, %	−0.144	**−0.325**	**−0.495***	−0.039	**−0.423****	**−0.562****	**−0.714****	**−0.429****
FRC, % (predicted)	0.006	**0.419***	**0.633****	0.128	−0.030	**0.602****	0.340	**0.382***
TLC, % (predicted)	−0.062	0.108	**0.465***	−0.074	0.057	**0.621****	**0.380***	**0.416****
D_LCO, % (predicted)	0.168	−0.144	−0.079	−0.194	−0.114	**−0.361***	**−0.401***	**−0.428****

CT, computed tomography; %LAA950, the percentage of lung voxels with a CT attenuation value < −950 HU on an inspiratory CT scan, represents the percentage of emphysema in the lung; %LAA856, the percentage of lung voxels with a CT attenuation value < −856 HU on an expiratory CT scan, represents the percentage of gas trapping in the lung; AwNS-IRAO, asthmatics with nonsmoking incomplete reversibility of airway obstruction; AwS-IRAO, asthmatics with smoking IRAO; BD, bronchodilator; D_LCO, single-breath diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; TLC: total lung capacity. Spearman correlation coefficient: *$p < 0.05$, **$p < 0.005$. Statistically significant correlations appear in bold.

We observed a stronger correlation between radiological features and lung function parameters in AwS-IRAO subjects. In addition, as expected, correlations between quantitative measures of emphysema and lung volumes or D_LCO were stronger in AwS-IRAO, whereas correlations between gas trapping and lung volumes were observed in both groups. In a heterogeneous group of smoking and nonsmoking subjects with asthma and airflow limitation, Hartley et al. [45] recently reported that air trapping was a significant predictor of lung function impairment. In contrast, they observed no significant correlation between emphysema and airflow limitation in the same group of subjects. This may mean that physiological changes are more related to the airway structure itself in smoking-related IRAO while for nonsmokers, other factors may play a role, such as different airway inflammatory features (as supported by our present data) or airway smooth muscle function [45].

Up to now, only 2 studies compared smoking from nonsmoking asthmatic patients with incomplete reversibility of airway obstruction but reported only qualitative data [25, 29]. Most of the other more extensive studies have compared ACO with "classical" COPD, showing that CT features are different between these 2 entities and strengthening the idea that ACO is a phenotype distinct from COPD [26, 46–48]. However, the definition of ACO varied among these studies [46, 48], particularly in regard to smoking history [26, 47].

Smoking influences the clinical presentation and prognosis of asthma. We recently reported that there were marked differences in clinical and physiological features between smoking and nonsmoking-related IRAO, suggesting that these 2 groups of subjects represent 2 different entities [20]. So, not only do clinical and physiological changes seem different in both groups, but our study suggests that underlying mechanisms are different, possibly because of differences in inflammatory phenotypes.

Although we found no absolute increase in neutrophils in AwS-IRAO, possibly due to the fact that most were ex-smokers, we showed that airway neutrophils were associated with emphysema in AwS-IRAO, as in "classical" COPD. This may be related, as in COPD, to their production of various elastases in addition to an increase in oxidative stress [49, 50]. Of interest, however, in AwNS-IRAO, the structural lung changes, in addition to airway wall thickening, were correlated with airway eosinophilia. We and others have shown emphysematous changes in nonsmoking asthma [51], possibly due to the influence of eosinophils. It has indeed been proposed that the production of the cytokine IL13 could be involved in this relationship [19, 52]. Eosinophils could also contribute to airway wall thickening through the release of various growth factors or deposition of extracellular matrix components [53, 54]. Our observations suggest that neutrophils have either an additive or predominant effect over eosinophils on lung parenchymal changes in smoking asthma while eosinophils are the main driver of both airway and lung parenchymal changes in nonsmoking asthma. However, these observations need to be further substantiated.

Among strengths of this study are the well-characterized population studied and the state-of-the-art CT assessment, including both quantitative and qualitative measures, performed by experienced imagers (H.C. and C.H., respectively). Finally, this is the first study to look at the airway inflammatory phenotype in relationship with structural and airway changes in the 2 groups studied.

Potential weaknesses of the study include its cross-sectional design in a limited number of patients, although the sample size was sufficient to document correlations between various parameters. We recognize that the significant proportion of ex-smokers in the AwS-IRAO group could have influenced some measures, particularly airway wall features. However, these were not different on sub-analysis between smokers or ex-smokers with IRAO.

Our study is the first to compare quantitative and qualitative CT features of asthma patients with a fixed component of airway obstruction according to their smoking status. Quantitative CT and visual evaluation, as performed in our study, may provide complementary, independent assessments of severity of emphysema, particularly in those with less severe abnormality, such as in our population of patients [55]. In this regard, Gietema et al. [56] found that in less severe categories of emphysema, radiologists tend to visually underestimate the extent of emphysema compared with quantitative measures, while in those with more severe emphysema, they may overestimate emphysema extent. Nevertheless, regardless of disease severity, Gietema reported that visual analysis of emphysema does not only show the extent of LAA but also lesion size, predominant emphysema type, distribution of emphysema, and presence/absence of areas of small airways disease [56]. Thus, our results are in keeping with this by showing that the extent, the distribution, and type of emphysema are different in 2 subpopulations of asthmatics with IRAO according to cigarette smoking status.

The qualitative scoring system we used defined trivial emphysema as a percentage that can reach as much as 25% emphysema. In a previous study, Gietema et al. [56]

defined trivial emphysema as <5% emphysema, which might be more appropriate . While we recognize that our scoring system could have underestimated the qualitative extent of emphysema, particularly in AwS-IRAO, our conclusions would remain the same.

Furthermore, some authors prefer to use the lower limit of normal value (LLN) to assess airway obstruction [57, 58]. However, many recent studies still use fixed criteria (0.7 for FEV_1/FVC ratio) and we also added the criteria of having an FEV_1 <80% to define IRAO. Hence, very few subjects had FEV_1/FVC higher than LLN (data not shown), and using LLN instead of the fixed ratio did not change our conclusions. Finally, we did not add a group of patients with COPD to the study as other authors have already compared CT features in patients with AwS-IRAO or asthma without IRAO and those with COPD [25, 26, 45, 46, 48, 59].

Conclusion

This study provides a detailed qualitative and quantitative analysis of bronchial and parenchymal features assessed on chest CT scans in smoking compared to nonsmoking asthmatics with fixed airway obstruction. Our results suggest that patients with chronic airway obstruction without a significant smoking history share several CT features with those that have a significant smoking history but that signs of mild emphysema are more prevalent and differently distributed in AwS-IRAO. There is, however, a correlation between airway neutrophilia and emphysematous features in AwS-IRAO and between eosinophilia and both airway wall thickness and emphysematous changes in nonsmoking asthma with IRAO. Therefore, the mechanisms leading to fixed airway obstruction and parenchymal changes may therefore be different between smokers and nonsmokers. As smoking in young asthmatics is unfortunately still quite prevalent, our study stresses the importance of smoking cessation early in asthma history [60].

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Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Conflict of Interest Statement

L.P.B. considers having no conflict of interest in regard to this publication. M.E.B., H.O.C., C.J.H., J.M., and J.L. have no conflicts of interest to declare. F.M. considers having no conflict of interest but wishes to declare what can be perceived as potential conflicts of interest: received fees for speaking at conferences sponsored by Boehringer Ingelheim, Novartis, and Grifols; research grants for participating in multicentre trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, and Novartis; and unrestricted research grants from Boehringer Ingelheim, Novartis, and Grifols.

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Author Contributions

M.E.B., F.M., and L.P.B. contributed to conception and design of the study. J.M., J.L., L.B., F.M., and L.P.B. contributed to collection of data. M.E.B., H.C., C.H., and L.P.B. contributed to analysis and interpretation of data. L.P.B., M.E.B., and H.C. contributed to writing of the manuscript. All authors reviewed the manuscript and approved its final version. L.P.B. is the guarantor of this study.

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