

ORIGINAL ARTICLE

Can computed tomography and carbon monoxide transfer coefficient diagnose an asthma-like phenotype in COPD?

FEISAL A. AL-KASSIMI,¹ ESAM H. ALHAMAD,¹ MOHAMMED S. AL-HAJJAJ,¹ EMAD RADDAOUI,^{2,3}
ABDULAZIZ H. ALZEER,⁴ AHMAD A. ALBOUKAI,⁵ ALI M. SOMILY,³ JOSEPH G. CAL,¹ ABDALLA F. IBRAHIM¹
AND SHAFFI A. SHAIK⁶

¹Department of Medicine, ³Department of Pathology, ⁴Critical Care Department, ⁵Department of Radiology, ⁶Department of Family and Community Medicine, King Saud University and ²Department of Pathology, Alfaisal University, Riyadh, Saudi Arabia

ABSTRACT

Background and objective: Post-mortem and computed tomography (CT) studies indicated that emphysema is a feature of COPD even in the 'blue bloater/chronic bronchitis' type. We aim to test the hypothesis that the non-emphysematous patients are distinct from the main body of COPD and are more akin to asthmatic patients.

Methods: We studied 54 patients with COPD. Emphysema was measured by Goddard's visual scoring of CT scan and the carbon monoxide transfer coefficient (KCO). Bronchial biopsy was offered for thickness of basement membrane (BM) ($\geq 7 \mu\text{m}$) as a marker of remodelling in irreversible asthma. Spirometry was repeated after therapy with Budesonide/Formoterol for 1 year.

Results: The non-emphysematous phenotype were 24 of 54 patients (44%) by CT scan and 23 of 54 patients (43%) by KCO, showing agreement in 53 out of 54 patients. The non-emphysematous patients were younger, had higher forced expiratory volume in 1 s (FEV₁) (median 61% vs 49.7%), greater prevalence of hypertrophy of nasal turbinates and higher serum IgE. The emphysematous phenotype had lower BMI and greater dyspnoea score. The BM was thickened in 11 of 14 and 0 of 10 patients in the non-emphysematous and emphysematous groups, respectively. Three patients without emphysema and a normal BM normalized their FEV₁ upon receiving inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA). All the non-emphysematous improved their FEV₁ after ICS/LABA (median = 215 mL). The median decline in the emphysematous was -65 mL.

Conclusion: The non-emphysematous phenotype of COPD displays important features of asthma: clinical picture, histology and response to ICS. CT and KCO can predict spirometric response to ICS/LABA.

SUMMARY AT A GLANCE

We aimed to compare the emphysematous and the non-emphysematous phenotypes of COPD, and to test the hypothesis that the latter has similarities with asthma. We found that the non-emphysematous phenotype displayed the following features of asthma: clinical picture, higher serum IgE, bronchial histology and response to inhaled corticosteroid.

Key words: asthma, chronic obstructive pulmonary disease, emphysema, radiology and other imaging.

Abbreviations: bd, Twice daily; BM, basement membrane; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DL_{CO}, carbon monoxide diffusion capacity; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRCT, high-resolution CT; HU, Hounsfield unit; ICS, inhaled corticosteroid; Ig, immunoglobulin; KCO, carbon monoxide transfer coefficient; LABA, long-acting β_2 agonist; MMRC, Modified Medical Research Council; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen.

INTRODUCTION

The first use of the term COPD is attributed to William Briscoe in discussion at the 9th Aspen Emphysema Conference.¹ In 1965, Briscoe and Nash divided COPD into emphysematous, bronchitic and intermediate groups.² These early concepts based on the differentiation of COPD were superseded and nowadays COPD is defined in terms of irreversibility of spirometric airways obstruction combined with symptoms. However, COPD is a heterogeneous condition displaying many phenotypes.^{3,4} These phenotypes are defined in terms of HRCT picture (emphysema dominant vs non-emphysematous alternately called airways dominant), endobronchial histology or cellular reaction

Correspondence: Feisal A. Al-Kassimi, Department of Medicine, King Saud University, P.O. Box 94357, Riyadh 11693, Saudi Arabia. Email: falkassimi@yahoo.com

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(eosinophilic vs non-eosinophilic).^{4–9} The COPD phenotypes were demonstrated to predict the clinical manifestations and response to inhaled corticosteroid (ICS).^{3–9}

The non-emphysematous phenotype of COPD is particularly worthy of interest for the following reasons. First, post-mortem studies showed that both 'pink puffer' and 'blue bloater' types of COPD displayed the same amount of emphysema at the time of death.¹⁰ This implies that the non-emphysematous phenotypes do not belong to either clinical forms of COPD. Second, other studies reported marked reduction of carbon monoxide diffusion capacity (DL_{CO}) (a strong marker of emphysema) in COPD patients displaying the clinical picture of chronic bronchitis including chronic purulent expectoration.¹¹ This is corroborated by HRCT reports which identify a phenotype of mixed bronchial thickening and emphysema in patients with a clinical picture of chronic bronchitis.⁴ The non-emphysematous phenotype is therefore unlikely to be a chronic bronchitis form of COPD. Finally, several studies indicated that the non-emphysematous COPD displayed clinical and haematological features of asthma such as eosinophilia, raised serum IgE and having received a physician diagnosis of asthma.^{4–6}

Guidelines are in agreement that irreversible asthma is the most important differential diagnosis of COPD.¹² The differentiating points (clinical picture, age of onset and spirometric reversibility) suffer from lack of specificity and overlap of end points.¹³ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that 'the degree of reversibility has never been shown to add to the diagnosis, differential diagnosis with asthma or to predicting the response to long-term treatment with bronchodilators or ICS'.¹²

The aim of our study is to compare the emphysematous and the non-emphysematous phenotypes. We hypothesize that the latter would display the cardinal features of asthma: clinical picture, bronchial histology and response to ICS.

METHODS

Patient selection and pulmonary function tests

The study was conducted at the teaching hospital of King Saud University, Riyadh, Saudi Arabia, between 2011 and 2015 on all consecutive patients with COPD. The study's protocol was approved by the Clinical Ethics Committee of the university as a prospective descriptive study and written informed consent was obtained from all patients and only one was lost to follow-up. The criteria are age 40 or above, history of chronic cough and dyspnoea, cigarette smoking of at least 10 pack-years, forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 70% and FEV_1 < 80% predicted or emphysema diagnosed by computed tomography (CT) scan involving five lobes of the lung regardless of spirometric values. Severe emphysema is documented to occur in the absence of FEV_1 or FEV_1/FVC abnormality.¹⁴ ICS was discontinued for 4 weeks. Tiotropium (Spiriva Handihaler; Boehringer Ingelheim,

Ingelheim, Germany) 18 µg once daily was prescribed. Spirometry was performed with reversibility test. DL_{CO} and carbon monoxide transfer coefficient (KCO), and arterial blood gases were also analysed. A KCO < 80% predicted was considered indicative of emphysema. This was followed by HRCT scan of the lungs. Bronchoscopic endobronchial biopsy was offered to all patients whose arterial partial pressure of oxygen (PaO_2) is >60 mm Hg. The above-described protocol has been in use since 2009 at the COPD clinic in our hospital for differentiating asthma from COPD.¹⁵ This was prompted by reports of clinical misdiagnosis of asthma and COPD, casting doubt on the validity of clinical differentiation.^{13,16,17} As long-acting β_2 agonists (LABAs) are not licensed for single use in Saudi Arabia, all patients were started on Budesonide 320 µg/ Formoterol 9 µg (Symbicort Turbuhaler; AstraZeneca, London, UK) bd. Salbutamol 200–400 µg (Ventolin inhaler; GlaxoSmithKline, Brentford, UK) as required was also prescribed. Guided by the response to a 12-month trial of ICS/LABA and results of the above-described investigations, further therapy was aimed at an asthma or COPD phenotype.¹⁵

Spirometry was repeated 4–6 monthly at least 2 months outside exacerbations. Budesonide/Formoterol was discontinued for 12 h and Salbutamol for 6 h prior to the test. Tiotropium was continued regardless of spirometry testing and was a constant before and after the administration of Budesonide/Formoterol. The values of FEV_1 reported are all post-bronchodilator.

Bronchial histopathology

Fibre optic bronchoscopy was performed for the 24 patients who consented to the procedure. Five biopsies were taken from a lobar bronchus of the lower lobe. Fixation was followed by embedding and staining with haematoxylin-eosin. This was followed by periodic acid-Schiff and trichrome staining for the basement membrane (BM). All slices were examined by point-to-point measurements of the BM at regular intervals of 20 µm as described by Sullivan *et al.*¹⁸ A computerized image analyser was used for measurements. Two observers (the pathologist and F.A.A.-K.) jointly ensured the proper orientation of the biopsy and placement of the ruler's end on the edges of the BM. The minimum length of the specimens examined was 800 µm.

HRCT scan scoring of emphysema

HRCT scanning was used (LightSpeed 16 or VCT XT; GE Medical Systems, Milwaukee, WI, USA). Full-volume acquisitions reconstructed for every 2.5 mm were obtained throughout the entire thorax. Images were acquired employing a standard window setting (window level: –700 Hounsfield units (HU); window width: 1500 HU). We used Goddard's quantitative visual scoring of emphysema (defined as areas of attenuation of the lung parenchyma).¹⁹ Zero represented no abnormality; 0.5 score was given for 1–5% involvement; 1 was given for 6–25% involvement; 2 for 26–50%; 3 for 51–75% and 4 for 76% or more.

Table 1 Characteristics of both groups

	No emphysema (<i>n</i> = 24)	Emphysema phenotype (<i>n</i> = 30)	<i>P</i> -value
Age (years)	60.0 (14) (41 to 77)	64.5 (10) (52 to 85)	0.007
Hypertrophy of nasal turbinates, <i>n</i> (%) [†]	21 (87.5)	7 (23.3)	<0.0001
Age at onset of chronic cough (years)	45.5 (16) (25 to 61)	51.5 (14) (35 to 71)	0.02
Age at onset of wheeze or dyspnoea (years)	46.5 (18) (25 to 69)	57 (11) (44 to 76)	0.003
Smoking (pack-years)	44 (49) (15 to 120)	70 (22) (42 to 140)	0.002
BMI (kg/m ²)	29.4 (10.7) (20.3 to 59.5)	27.25 (9.5) (19 to 40)	0.002
MMRC dyspnoea score	1 (1) (1 to 2)	3 (2) (2 to 4)	<0.0001
Baseline pulmonary function test			
FEV ₁ (% predicted)	61.0 (19.0) (37 to 78)	49.0 (18.5) (28 to 80)	0.008
DL _{CO} (% predicted)	79 (19) (50 to 105)	37 (17) (16 to 74)	<0.0001
KCO (% predicted)	110.5 (30.3) (85 to 144)	56.0 (19.5) (23 to 90)	<0.0001
Arterial blood gas			
PaO ₂ (mm Hg)	77.5 (7.8) (64 to 100)	65.0 (14.0) (49 to 79)	<0.0001
PaCO ₂ (mm Hg)	40 (3.8) (31 to 56)	43 (9.3) (35 to 70)	0.049
Serum IgE (kU/L)	251.5 (1259) (15.1 to 5000)	116.0 (228.3) (5.5 to 3975)	0.047
Reticular BM (μm)	8.4 (2.2) (4.05 to 13.1)	5.2 (1.6) (2.6 to 6.4)	0.001
Change in FEV ₁ (%) [‡]	9.75 (12.2) (1.5 to 45)	-4.4 (3.4) (-19 to 17.8)	<0.0001
Change in FEV ₁ (mL) [‡]	215 (264) (30 to 640)	-65 (52) (-290 to 40)	<0.0001

Data are presented as medians (interquartile range), (range) or numbers (with percentages). All comparisons were done by Mann-Whitney U-test.

[†]Comparisons were done by chi-square test.

[‡]Change in FEV₁ after 1 year of ICS/LABA.

BM, basement membrane; DL_{CO}, carbon monoxide diffusion capacity; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; KCO, carbon monoxide transfer coefficient; LABA, long-acting β₂ agonist; MMRC, Modified Medical Research Council; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen.

Three observers (a radiologist and two clinicians) scored three cuts at the following levels: arch of the aorta, bifurcation of the trachea and one cut above the diaphragm. Emphysema was considered significant if the average score was ≥1. This was based on reports by that the lowest 25% percentile for emphysema displays features for asthma.⁶ Consensus was used to smooth out any inter-observer differences.

Statistical analysis

Medians, interquartile range and range were used to describe the study variables. The non-parametric Mann-Whitney U-test was used to compare the median values. The chi-square test was used to observe an association between categorical items and outcome variables. A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 54 patients (53 had airway obstruction and one had emphysema with FEV₁ of 80% predicted) were included. The non-emphysematous phenotype included 24 of 54 patients (44%) by HRCT and 23 of 54 patients (43%) by KCO, showing agreement in 53 out of 54 patients between the two techniques. Table 1 shows the differences between the two groups. The non-emphysematous patients were significantly younger on presentation and at the onset of symptoms. They were also more likely to have

hypertrophy of the nasal turbinates and higher serum IgE level. Although their FEV₁ was higher, 7 of 24 patients (29%) had an FEV₁ ≤ 50% predicted. KCO was normal (≥80% predicted) in all the non-emphysematous phenotypes. Lastly, they had higher PaO₂ and lower arterial partial pressure of carbon dioxide (PaCO₂), and only one patient in the non-emphysematous group had hypercapnia. He had a BMI of 59.5 kg/m², PaO₂ of 64 mm Hg and Pa CO₂ of 56 mm Hg and was already diagnosed as obesity hypoventilation syndrome.

The emphysematous group was older with lower FEV₁ and BMI and greater dyspnoea score. They all had a low KCO except for one patient whose emphysema score was only 1.16 and his KCO was 90% predicted. This patient was the only one in the emphysematous group to display a positive response to ICS, raising the possibility of misclassification by HRCT.

Figure 1 shows that the BM was thickened in 11 of 14 and 0 of 10 patients in the non-emphysematous and emphysematous groups, respectively. The three non-emphysematous patients who had no increase in their BM thickness had an FEV₁ of 75–78% predicted and normalized their FEV₁ fully upon receiving ICS.

Figure 2 shows the response of FEV₁ value following therapy with Budesonide/Formoterol for 1 year in both groups, as classified by HRCT and KCO, respectively. All the non-emphysematous patients had a positive response. However, all the emphysematous patients showed a decline or a non-significant rise of FEV₁ except for one patient who had a borderline

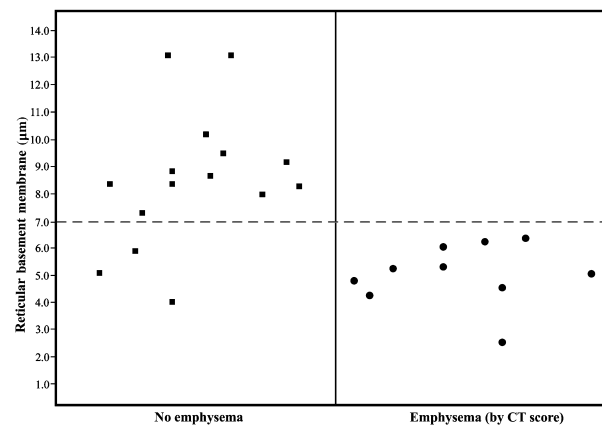


Figure 1 Thickness of reticular basement membrane in both groups. The grouping is based on computed tomography (CT) score.

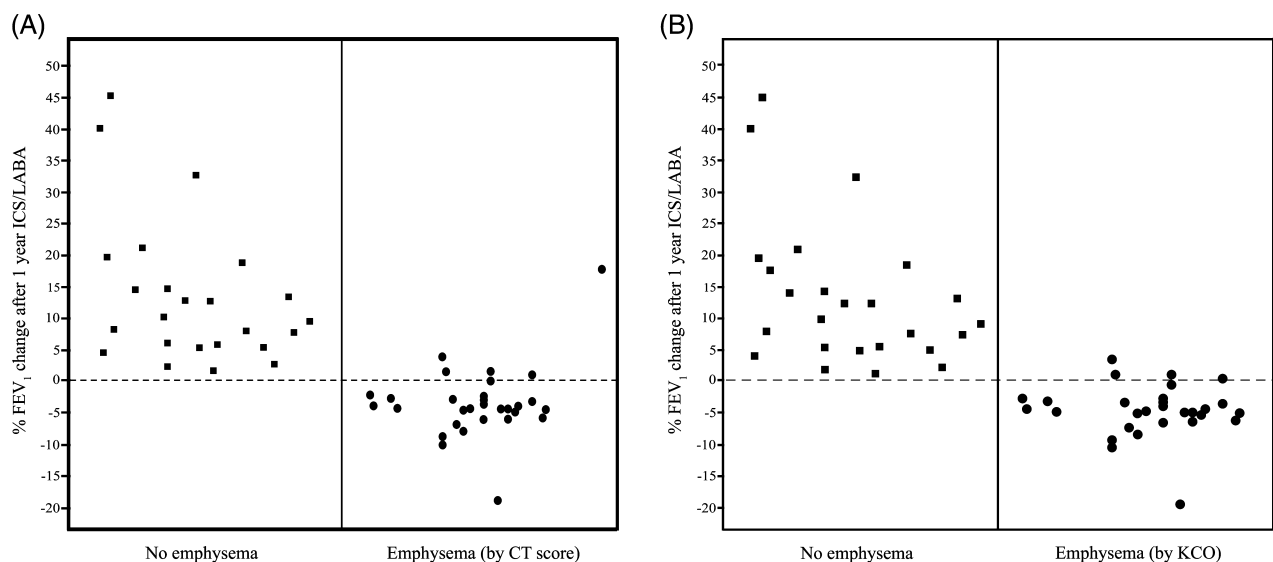


Figure 2 (A) Response to inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) in both groups. The grouping is based on computed tomography (CT) score. (B) Response to ICS/LABA in both groups. The grouping is based on carbon monoxide transfer coefficient (KCO).

emphysema score and a KCO of 90% predicted. The median improvement of FEV_1 in the non-emphysematous group was 215 mL (range: 30 to 640) as opposed to a decline of -65 mL (range: -290 to 40) in the emphysematous group in spite of therapy with Budesonide/Formoterol for 1 year. Figure 3 contrasts two patients with a similar FEV_1 and different phenotypes.

DISCUSSION

The main finding is that non-emphysematous COPD (by HRCT or KCO) displays significant differences from the emphysematous phenotype and similarities with asthma. There are two techniques for the diagnosis of emphysema by CT scan: computed densitometry and visual scoring. Although visual scoring has been reported to give rise to inter-observer

discrepancies,²⁰ we believe it to be superior to densitometry. Various studies on densitometry used a wide range of lung attenuation values (-820 to -950 HU) and divergent percentiles of lung involvement to diagnose emphysema.²¹ More importantly, computed densitometry is reported to overlap severe irreversible asthma and COPD.²² The concordance of visual scoring with KCO and response to ICS (reported in this study) supports the suitability of the technique for phenotyping. It is possible that the use of a consensus scoring smoothed out the inter-observer differences.

The non-emphysematous phenotype was reported in 10–38% of COPD series.^{5,23,24} However, divergent methodology and clinical settings (primary care vs referral centres) make the comparison difficult. Although previous studies concur with our finding of higher FEV_1 in the non-emphysematous phenotype, it is not merely an early stage of COPD.^{5,23,24} In a large

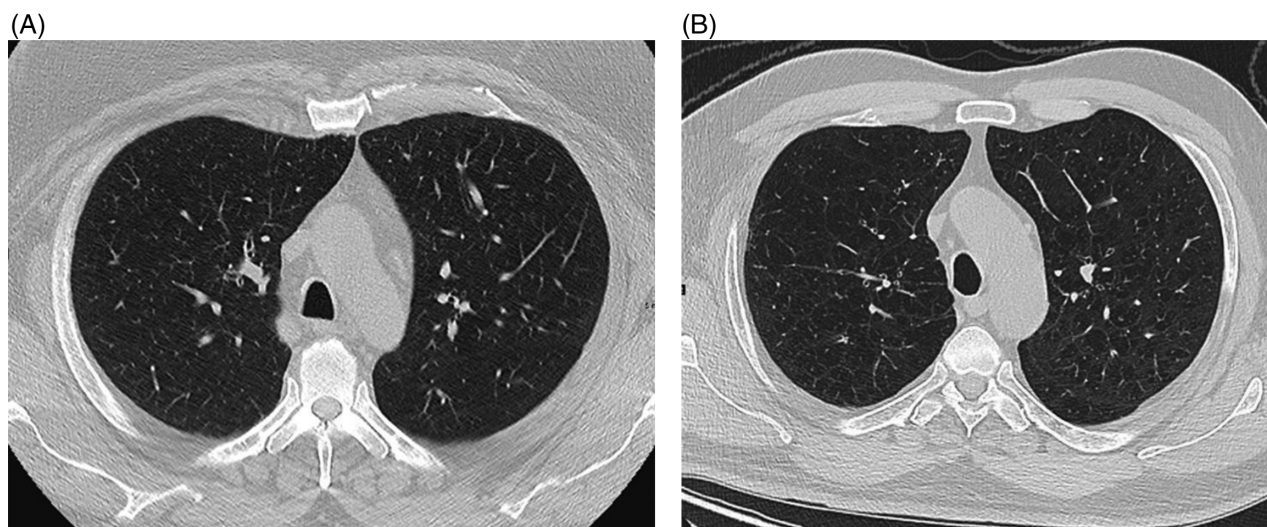


Figure 3 (A) Non — emphysematous phenotype, forced expiratory volume in 1 s (FEV_1) = 42% predicted, emphysema score = zero, dyspnoea score = 2, basement membrane (BM) = 8 μ m and FEV_1 response to inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) = 18.6% or 220 mL. (B) Emphysematous Phenotype, FEV_1 = 41% predicted, emphysema score = 3.3, dyspnoea score = 4, BM = 5.4 μ m and FEV_1 response to ICS/LABA = a decline of 6.1% or -70 mL.

Japanese study, the non-emphysematous group was well represented in all stages of COPD.²⁴ Similarly, previous studies concur with our findings that emphysematous patients have lower BMI, greater hypoxaemia and hypercapnia and higher dyspnoea score.^{5,7,23,24} Emphysema, even in the absence of airway obstruction, was also associated with a more rapid annual decline of FEV_1 .²⁵

Although a recent report described mild, microscopic emphysema in non-smoking asthmatic patients, all three patients had normal KCO without emphysema on CT scan.²⁶ Occasionally, mild focal emphysema was reported by CT scan in non-smoking severe asthmatic patients.²⁷ However, reports are unanimous on the fact that gross or diffuse emphysema is not a feature of asthma as documented by CT scan even in severe or neutrophilic asthma.^{28–30} Similarly, KCO remains normal or raised even in severe asthma.^{28–30}

We are aware of a few reports of an association between non-emphysematous picture by CT scan and both bronchial histology and a positive response to ICS. Al-Kassimi *et al.* reported in 2011 on a group of smokers with irreversible airway obstruction who were classified as irreversible asthma and COPD mainly on the basis of HRCT and bronchial biopsy.¹⁵ In that study, the non-emphysematous group was associated with hypertrophy of nasal turbinates, histology of asthma, normal KCO and response to ICS supporting an asthmatic origin.¹⁵ Chanez *et al.* reported in 1996 that 12 of the 25 (48%) COPD patients responded to a trial of oral prednisolone and their bronchial biopsies displayed uniform thickening of the BM.⁸

Studies on asthmatic patients with mild reversible asthma concluded that bronchial biopsy could not differentiate asthma from COPD.^{31,32} However, the technique was reported to be highly useful when applied to the irreversible form of asthma. In Fabbri *et al.*'s study on the pathology of COPD and irreversible asthma (with

a mean post-bronchodilator FEV_1 of 62% predicted), the BM thickness was 6.6–7.4 μ m in asthmatic patients and 4.2–6.2 μ m in COPD patients without overlap.³³ Similarly, there was no overlap of the BM thickness in Al-Kassimi *et al.*'s study on COPD patients who were divided into irreversible asthma and COPD proper.¹⁵ Bourdin *et al.* studied 150 patients with mild asthma, severe asthma and COPD and concluded that the BM thickness can be considered 'a hallmark of severe disease'.³⁴ They found that a threshold of 6.65 μ m differentiated severe asthma from COPD with a sensitivity of 89% and specificity of 68%.³⁴ The findings in our study are in line with the above-described conclusions: all patients with BM ≥ 7 μ m had no significant emphysema on CT scan and responded to ICS. Also, all patients with emphysema had no thickening of the BM.

Various workers have estimated that 33–48% of patients with COPD suffer from asthma.^{8,15,35} The differentiating points suffer from lack of specificity and overlap of end points.¹³ This is not surprising if we consider the following: First, reports indicate considerable misdiagnosis of asthma and COPD by clinicians.^{16,17} Second, asthma in adulthood may manifest with fixed obstruction, whereas a considerable reversibility may be observed even in subjects without a prior history of asthma in COPD.³⁶ Third, 'reversibility' is not a dichotomous trait and within-subject variability is considerable both in asthma and COPD.^{37,38} Calverley *et al.* reported that 52% of COPD patients changed reversibility status between visits.³⁸

Asthma of middle-aged and the elderly patients is characterized by being less atopic, less labile and more likely to be progressive and irreversible.^{13,39} Smoking and rhinitis, even in the absence of atopy, are important associations.^{40,41} The chronic irreversible nature and association with smoking may explain the difficulty of differentiating adult-onset asthma from COPD.

Asthma in the elderly patients is frequently unrecognized and inadequately treated.⁴² The prevalence of asthma above the age of 65 years is estimated between 6.5% and 17%.³⁹ The Copenhagen City Heart Study reported on newly diagnosed asthma during a 10-year follow-up in a sample comprising 4983 individuals.⁴³ In that study, the proportion of newly diagnosed asthma was same in all the age groups: 7% at age >64 years, 7% at age 35–64 years and 6% at age <35 years.⁴³

As early as 1999, Davies *et al.* reported a correlation between DL_{CO} and response to ICS in COPD.⁴⁴ We believe that CT scan and KCO are the ideal techniques for phenotyping. Bronchial biopsy is safe but invasive, and sputum eosinophilia requires special laboratory techniques.

Many authors have called for phenotype-guided therapy in COPD,^{3,35,45,46} and highlighted the lack of response to ICS in the emphysematous phenotype.^{3,7,35} Lee *et al.* reported no improvement of FEV₁ after 3 months of therapy with ICS/LABA.⁷ Al-Kassimi *et al.* found no decline of FEV₁ on abrupt withdrawal of ICS in the emphysematous phenotype.⁴⁷ A review of the literature concluded that whenever phenotyping was applied, COPD split into responsive and non-responsive entities along predictable fault lines of radiology, pathology or cellular reaction.⁴⁸

The limitation of our study is the small number of patients. Our findings should be repeated in larger studies.

In conclusion, the non-emphysematous phenotype of COPD displays the cardinal features of irreversible adult-onset asthma. Phenotyping by CT scan or KCO could streamline therapy in COPD and predict the spirometric response to ICS.

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Disclosure statement

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