Asthma Masquerading as Chronic Obstructive Pulmonary Disease: A Study of Smokers Fulfilling the GOLD Definition of Chronic Obstructive Pulmonary Disease

Feisal A. Al-Kassimi^a Abdullah A. Abba^a Mohammed S. Al-Hajjaj^a
Esam H. Alhamad^a Emad Raddaoui^b Shaffi Ahamed Shaikh^c

Departments of ^aMedicine, ^bPathology and ^cFamily and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Key Words

Airway obstruction • Asthma • Bronchial biopsy • Chest CT • Chronic obstructive pulmonary disease • Differential diagnosis • Global Initiative for Obstructive Lung Disease guidelines

Abstract

Background: Irreversible airways obstruction in smokers is usually attributed to chronic obstructive pulmonary disease (COPD). We speculate that some of these are cases of asthma indistinguishable from COPD. **Objectives:** To determine the prevalence of asthma in a 'COPD' population and how to differentiate the two conditions. **Methods:** This was a prospective observational study of smokers fulfilling the Global Initiative for Chronic Obstructive Lung Disease definition of COPD [mean post-salbutamol forced expiratory volume in 1 s (FEV₁) 66.9% predicted]. They were classified into 4 groups, as follows: (1) inhaled corticosteroid (ICS)-responsive asthma, defined by normalization of spirometry upon ICS treatment; (2) irreversible asthma, defined as airway obstruction for 1 year and bronchial biopsy indicating asthma; (3) COPD, in the presence of bilateral panlobular emphysema with bullae on high-resolution computed tomography, hypercapnic respiratory failure or bronchial biopsy indicating

COPD, and (4) unclassified airflow limitation (AFL). **Results:** Eighty patients fulfilled the definition of COPD. The initial diagnosis was COPD in 57.5% and asthma in 42.5%. The final diagnosis was ICS-responsive asthma in 48 patients (60%), irreversible asthma in 8 (10%), COPD in 16 (20%) and unclassified AFL in 8 (10%). A normal transfer coefficient for carbon monoxide (KCO) and an FEV₁ fluctuation $\geq 18\%$ during 1 year of follow-up distinguished irreversible asthma and COPD. Seven of the 8 patients with irreversible asthma had improved FEV₁ at the end of 1 year (median 320 ml compared with –29 ml in COPD). Five out of the 8 unclassified AFL cases had normal KCO and a large improvement in FEV₁ suggestive of irreversible asthma. **Conclusions:** COPD, even in heavy smokers, includes cases of asthma. FEV₁ fluctuation during 1 year is a novel concept which may distinguish irreversible asthma and COPD.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the commonest respiratory illnesses, with high morbidity. Misdiagnosing one condition as the other is not uncommon, especially in the elderly [1–3]. Bellia

et al. [2], in 2003, found that every fifth elderly asthmatic patient is misdiagnosed as having COPD. In another study on 25 patients labeled as having COPD, 12 were proven conclusively to be asthmatic [3]. Large studies have documented that diagnostic confusion between the two conditions is common [4] and that the label can be switched between COPD and asthma in the same patient [5]. The various guidelines on both sides of the Atlantic [e.g. Global Initiative for Chronic Obstructive Lung Disease (GOLD), National Institute for Health and Clinical Excellence, American Thoracic Society/European Respiratory Society] recognize the presence of irreversible asthma but do not offer conclusive means of differentiating it from COPD. The American Thoracic Society/European Respiratory Society guidelines stated in 2004 that 'some patients with asthma cannot be distinguished from COPD with the current diagnostic tests' [6]. More importantly, many authorities are still debating whether asthma and COPD are the same disease (the Dutch hypothesis) [7, 8]. However, the landmark work of Fabbri et al. [9] on the histology of asthma and COPD has opened the way for reliable differentiation between the two conditions with the help of bronchial biopsy.

COPD (diagnosed by spirometry criteria), when it occurs in never-smokers, is attributed in 20–80% of cases to irreversible asthma. This is concluded mainly on the basis of a history of asthma, eosinophilia or significant reversibility of forced expiratory volume in 1 s (FEV_1) [10, 11]. The term airflow limitation (AFL) is used by some researchers to describe airway obstruction of unknown etiology.

On the other hand, COPD in smokers is usually attributed to genuine COPD (chronic bronchitis/emphysema). We speculate that even in smokers there must exist a significant number of cases of irreversible asthma masquerading as genuine COPD, given 2 facts: (1) over 20% of cases of asthma become irreversible [12, 13] and (2) smoking increases the risk of irreversible asthma [13].

Therefore, we decided to study a group of smoking patients who fulfill the GOLD definition for COPD in order to explore (1) the relative prevalence of COPD, irreversible bronchial asthma, unclassified AFL (not classified as either irreversible asthma or COPD) and inhaled corticosteroid (ICS)-reversible bronchial asthma in the group of smokers, (2) noninvasive criteria for differentiating COPD and irreversible asthma and (3) the rate of FEV_1 decline in 1 year in irreversible asthma and COPD.

High-resolution computed tomography (HRCT) and bronchial biopsy were used as means of achieving the classification.

Fig. 1. Panlobular emphysema with bullae.

Methods

Study Population

This was a prospective observational study conducted between September 2007 and March 2009 at King Khalid University Hospital, Riyadh, Saudi Arabia. The study was approved by the Institutional Review Board of King Saud University, and all participants gave written informed consent. Patients attending the pulmonology clinics were screened, and those fulfilling the following criteria were enrolled in phase I of the study: smokers (>10 packs/year), age 40–70 years and labeled by their treating pulmonologist as having asthma or COPD. Exclusion criteria were bronchiectasis or left ventricular failure.

Pulmonary Function Testing

All patients underwent spirometry before and 15 min after inhaling 5 mg of salbutamol by nebulizer. This is the standard practice in our institution as many elderly patients have difficulty with the meter dose inhaler technique. Patients with FEV_1 /forced vital capacity <70% and FEV_1 <80% after salbutamol nebulization (GOLD stage II or worse) were enrolled for phase II. The patients were reviewed after 3 weeks and then every 2 months for 1 year with a repeat of pre- and post-salbutamol spirometry. Plethysmography and diffusing capacity for carbon monoxide (DL_{CO}) were performed at 0, 6 and 12 months. DL_{CO} was divided by lung volume to obtain the transfer coefficient for carbon monoxide (KCO). All tests were performed at least 1 month after the last acute exacerbation, defined as any worsening of symptoms requiring a visit to a doctor or a change of regular medications. The tests were performed according to the recommendations of the American Thoracic Society.

Patient Follow-Up and Diagnostic Criteria

Patients on metered dose inhalers were tested for inhalation technique. All patients were started on budesonide 320 µg/formoterol 9 µg twice daily by Turbuhaler (Symbicort; AstraZeneca,

Fig. 2. Flow diagram of diagnostic criteria. FVC = Forced vital capacity; LABA = long-acting β_2 -agonist.

Sweden) after tuition. A plain chest X-ray and HRCT scan were ordered, and patients free from bullous panlobular emphysema or hypercapnic respiratory failure were offered an endobronchial biopsy taken by fiberoptic bronchoscopy from a 3rd-order bronchus. Hypercapnic respiratory failure was defined as PaO_2 of 60 mm Hg or less, $\text{PaCO}_2 > 45$ mm Hg and bicarbonate > 28 mmol/l. The accuracy of HRCT, hypercapnic respiratory failure and bronchial biopsy to distinguish COPD and irreversible asthma is described below in the Discussion.

Panlobular emphysema was defined as extensive areas of low attenuation without a well-defined wall that are evenly distributed throughout the lobule and associated with vascular and septal disruption. Bullae are diagnosed when several of these areas exceed 2 cm in diameter (fig. 1). Centrilobular and paraseptal emphysema, which occasionally occur in asthma, were not accepted as evidence for COPD.

Figure 2 is a flow diagram for the diagnostic criteria. The final diagnosis was made according to the following classification:

- (1) ICS-responsive asthma if spirometry normalized with budesonide/formoterol at any time during follow-up;
- (2) irreversible asthma if spirometry remained obstructive during follow-up in spite of budesonide/formoterol and the bronchial biopsy showed diffuse thickening of the reticular basement membrane of at least $6.6 \mu\text{m}$ (fig. 3);
- (3) COPD in the presence of panlobular emphysema with bullae, hypercapnic respiratory failure or bronchial biopsy showing squamous metaplasia with epithelial/subepithelial inflammation and a basement membrane of $6.0 \mu\text{m}$ or less (fig. 4), or
- (4) unclassified AFL if the patient refused bronchial biopsy and continued to experience airway obstruction.

Management of Patients

All the patients in the study were managed as indicated by their clinical condition. It has been the practice in the first author's clinic to use HRCT scan and fiberoptic bronchial biopsy as means of differentiating irreversible asthma and COPD. The patients diagnosed with COPD were continued on budesonide/formoterol only if they had had frequent exacerbations (3 or more) in the previous year. Otherwise, anticholinergics were used instead.

Statistical Analysis

The data were entered in MS Excel and analyzed using the statistical software package SPSS PC+ version 13.0 (SPSS Inc., USA). Descriptive statistics, i.e. medians, interquartile range and range, were used to describe the study variables. Nonparametric statistical tests, i.e. the Mann-Whitney U test and Kruskal-Wallis test, were used to compare the median values across the categorical variables with 2 and 3 groups. The χ^2 test was used to observe an association between categorical study and outcome variables. A p value of < 0.05 was considered statistically significant.

Results

As seen from table 1, a total of 81 patients fulfilled the GOLD criteria for COPD (airway obstruction after salbutamol nebulization). One patient was lost to follow-up. All but 1 were male, and 70% had smoked 40 packs/year

Table 1. Characteristics of the patients

Age, years				
Mean $\pm$ SD		55.6 $\pm$ 8.92		
Range		40–70		
Gender				
Males		79 (98.75%)		
Females		1 (1.25%)		
Smoking history				
11–19 packs/year		6 (7.6%)		
20–29 packs/year		9 (11.2%)		
30–39 packs/year		9 (11.2%)		
40–49 packs/year		15 (18.8%)		
≥ 50 packs/year		41 (51.2%)		
Initial diagnosis				
BA		34 (42.5%)		
COPD		46 (57.5%)		
Final diagnosis				
ICS-reversible BA		48 (60.0%)		
Irreversible BA		8 (10%)		
COPD		16 (20.0%)		
Unclassified AFL		8 (10%)		

Severity by GOLD criteria (post-salbutamol)	ICS-reversible BA	Irreversible BA	COPD	Unclassified AFL
Stage II	46	7	11	6
Stage III or IV	2	1	5	2

Figures represent numbers of patients, except where indicated otherwise. BA = Bronchial asthma.

Table 2. Pre- and post-salbutamol spirometry for our 80 patients

	FEV ₁ , ml	FEV ₁ , % pred.	FEV ₁ /FVC, %
Pre-salbutamol	1,909 $\pm$ 503 (844–2,849)	61 $\pm$ 9.8 (32.7–76.2)	63 $\pm$ 4.6 (52.9–68.9)
Post-salbutamol	2,098 $\pm$ 581 (890–3,150)	66.9 $\pm$ 11.4 (32.9–78.1)	65.7 $\pm$ 4.8 (53–69.9)

Values are shown as means $\pm$ SD (range).
FVC = Forced vital capacity.

or more. Table 2 gives the spirometry values before and after salbutamol. A total of 70 patients were stage II (moderately severe) and 10 were stage III or IV (severe or very severe) according to GOLD criteria. Treatment compliance was poor, as only 12 of 80 (15%) were taking their medications regularly as prescribed; the rest were using their inhalers only once daily or as required. Moreover,

Fig. 3. Diffuse reticular basement membrane thickening in irreversible asthma. Periodic acid-Schiff stain. $\times 40$. **Fig. 4.** Squamous metaplasia with epithelial/subepithelial inflammation without thickening of the reticular basement membrane in COPD.

all the patients on metered dose inhalers had serious problems with inhalation technique, namely lack of hand-breath coordination or shallow inhalation.

The initial diagnosis was bronchial asthma in 42.5% and COPD in 57.5%. The final diagnosis was as follows: ICS-reversible asthma in 48 patients (60%), irreversible asthma in 8 (10%), COPD in 16 (20%) and unclassified

Table 3. Comparison of clinical characteristics and pulmonary function tests between 3 groups of patients**a Clinical characteristics**

Final diagnosis	ICS-reversible BA (n = 48)	Irreversible BA (n = 8)	COPD (n = 16)	p value
Age, years	52 (47–61) (40–70)	52.5 (44–56) (42–61)	67.5 (54–70) (49–70)	0.001 ^a
Smoking				
11–19 packs/year	5 (10.4%)	1 (12.5%)	0	
20–29 packs/year	9 (18.7%)	0	0	
30–39 packs/year	8 (16.7%)	1 (12.5%)	0	
40–49 packs/year	12 (25%)	3 (37.5%)	0	
≥50 packs/year	14 (29.2%)	3 (37.5%)	16 (100%)	
Age at onset of chronic cough, years	47.5 (41–53) (21–69)	39 (31–50) (22–52)	49.5 (44–55) (30–60)	0.16 ^a
Age at onset of chronic expectoration, years	47.5 (41–52) (21–69)	39 (36–50) (31–52)	49.5 (44–56) (30–60)	0.14 ^a
Age at onset of wheeze, years	45.5 (41–57) (17–69)	48.5 (33.5–53) (12–55)	60 (48–66) (40–69)	0.018 ^a
Age at onset of exercise intolerance/dyspnea, years	45.5 (41–56) (17–69)	48.5 (34–53) (12–55)	56 (47–60) (40–64)	0.049 ^a
History of allergic rhinitis	43 (89.6%)	8 (100%)	3 (18.8%)	<0.0001 ^b
Hypertrophy of nasal turbinates on examination	45 (93.8%)	8 (100%)	4 (25%)	<0.0001 ^b
Symptoms triggered by external triggers	38 (79.2%)	8 (100%)	10 (62.5%)	0.10 ^b
Increased anteroposterior diameter of chest	9 (18.8%)	6 (75%)	15 (93.85%)	<0.0001 ^b
Upper border of liver in 6th space or more	3 (6.2%)	3 (37.5%)	11 (68.8%)	<0.0001 ^b

Values are shown as medians (interquartile range) (range) or numbers of patients (percentage), as appropriate. BA = Bronchial asthma.

^a Kruskal-Wallis test. ^b χ^2 test.

b Pulmonary function tests

	ICS-reversible BA (n = 48)	Irreversible BA (n = 8)	COPD (n = 16)	p value
KCO, % predicted	93.9 (89–100.3) (79–116)	93.4 (84–98.18) (81.2–117.6)	48.9 (29.4–60) (18.7–65.3)	<0.0001 ^a
Greatest fluctuation in FEV ₁ in 1 year, %	–	29.4 (22.8–40.95) (18.1–50.5)	13.85 (9.73–15.1) (5.7–17.4)	<0.0001 ^b
Greatest fluctuation in FEV ₁ in 1 year, ml	–	580 (260–750) (250–880)	190 (120–280) (60–390)	<0.001 ^b
Change in FEV ₁ at the end of 1 year, ml	–	320.5 (57.5 to 460) (–260 to 500)	–29 (–48 to 45) (–120 to 91)	0.007 ^b

Values are shown as medians (interquartile range) (range). BA = Bronchial asthma.

^a Kruskal-Wallis test. ^b Mann-Whitney U test.

AFL in 8 (10%). The diagnosis of COPD was based on the following: bullous panlobular emphysema in 6 patients, hypercapnic respiratory failure in 4, bullae plus respiratory failure in 1 and bronchial biopsy in 5. Bronchial biopsy was performed in 13 patients. In the 8 patients with irreversible asthma, the mean basement membrane thickness was 7.76 μ m (range 6.6–8.7), compared with 4.86 μ m (range 3.7–5.9) in the 5 patients whose COPD was diagnosed by biopsy. The COPD patients had, in ad-

dition, squamous metaplasia with epithelial/subepithelial inflammation.

Table 3a compares the clinical characteristic of 3 groups (ICS-reversible asthma, irreversible asthma and COPD) based on final diagnosis. Patients with COPD were significantly older than those with ICS-reversible bronchial asthma and irreversible asthma. All COPD patients had smoked 50 packs/year or more, but heavy smoking was also found with bronchial asthma. The on-

Table 4. Characteristics of the undiagnosed AFL group

Age years	FEV ₁ after 3 weeks of ICS/LABA % predicted	KCO % predicted	FEV ₁ fluctuation during follow-up, %	Change in FEV ₁ at the end of 1 year, ml
54	63	86	18	350
55	75	89	40	480
45	67	87	32	600
60	43	92	21	260
60	53	95	29	320
53	78	51	11	-19
60	47	46	16	-44
70	56	55	7	35

LABA = Long-acting β_2 -agonist.

set of wheeze or shortness of breath was late in COPD; these 2 symptoms appeared in our COPD patients at age 40 or older. Allergic rhinitis and hypertrophy of nasal turbinates were significantly associated with reversible and irreversible asthma, but were occasionally present with COPD. None of the clinical features could differentiate the 3 conditions.

As seen in table 3b, KCO differentiated fully between COPD and irreversible asthma. Irreversible asthma showed much greater levels of fluctuation of FEV₁ and maximum expiratory flow at 50% of vital capacity in 1 year than COPD. Only the fluctuation of FEV₁% in 1 year distinguished irreversible asthma from COPD; a level of fluctuation of 18% or more occurred in all asthmatics and none in COPD. At the end of the 1-year follow-up, 7 of the 8 patients with irreversible asthma had increased their FEV₁ (median 320 ml). In the majority of COPD patients (12/16), FEV₁ had deteriorated (median change -29 ml), although only 2 of the 16 patients were still smoking.

Table 4 gives the characteristics of the undiagnosed AFL group. It is clear that the group is heterogenous and likely to contain both COPD and irreversible asthma cases. The first 5 patients had normal KCO and wider fluctuations of FEV₁ during follow-up than the asthmatics (above 18%), and all showed improvements in FEV₁ at the end of follow-up (range 260–600 ml). The last 3 patients had low KCO and less fluctuation of FEV₁ in 1 year, and their FEV₁ declined or rose very little (range -44 to 35 ml).

Although the two subgroups of patients with unclassified AFL behaved physiologically like irreversible asthma and COPD, we cannot conclusively ascribe a diagnostic label to them.

Discussion

This paper describes a simple clinical scheme aimed at elucidating the nature of cases of salbutamol-irreversible airways obstruction (fulfilling the GOLD definition of COPD). In spite of an abundance of publications on the role of HRCT scan and bronchial histopathology in differentiating COPD and asthma, there is surprisingly little use of these methods. The various guidelines on both sides of the Atlantic do not advocate their use in the differentiation of COPD from irreversible asthma.

Although many studies have documented that asthma and COPD have distinct bronchial pathologies, these studies suffered from the drawback that they compared old COPD patients with young patients with reversible asthma and concluded that the bronchial biopsy is not sufficiently discriminatory [14]. The paper of Fabbri et al. [9] in 2003 was a landmark, as it compared COPD with 'fixed' (irreversible) asthma in patients with an average age of 65 years. They concluded that in those groups, the two conditions are distinguishable pathologically. Thickening of the reticular basement membrane – the hallmark of chronic asthma – is associated with airway remodeling and irreversible asthma; studies in that group have documented the usefulness of basement membrane measurement [9, 15, 16]. In the paper of Fabbri et al. [9], the basement membrane in irreversible asthma was 6.6–9.7 μm , and in COPD, it was 4.2–6.2 μm [9]. Other pathological features, e.g. CD₄/CD₈ ratio, unlike thickness of the reticular basement membrane, showed an overlap between irreversible asthma and COPD [9]. Based on the work of Fabbri et al. [9] and others and our own observations, the most reliable and reproducible sign for asthma is uniform thickening of the reticular basement membrane of 6.6 μm or more [9, 15, 16], and for COPD, a basement membrane of 6 μm or less in addition to squamous metaplasia with epithelial/subepithelial inflammation [9, 15]. All our patients with irreversible asthma (diagnosed by biopsy) had normal KCO and significant reversibility of FEV₁, features that were absent in those patients diagnosed histologically as having COPD.

Large studies on patients receiving long-term oxygen for chronic respiratory failure in Italy and Poland included no asthmatics, and the commonest indication was COPD [17, 18]. Although hypercapnea with acidosis is common in acute severe asthma attacks, we found no reports of chronic hypercapnea with raised bicarbonate in stable asthma. We found a report where some elderly (average age 79 $\pm$ 1.2 years) Japanese subjects with irreversible asthma (average FEV₁ 55 $\pm$ 0.5% predicted) required

home oxygen therapy [10]. Even in that extreme group (in terms of age and FEV₁), the alveolar-arterial gradient for oxygen was only 22.1 ± 1.6 mm Hg, and PaO₂ was 76.9 ± 1.7 mm Hg. It is not mentioned why those patients required home oxygen and whether it was used intermittently for asthma exacerbations or continuously [10].

HRCT cannot always differentiate asthma from COPD, as mild emphysema has occasionally been reported in asthma [19, 20]. However, the emphysema associated with asthma is usually centrilobular or paraseptal and not panlobular [19, 20]. In the largest series of asthmatics (160 patients), 7.9% of patients had centrilobular or paraseptal emphysema, but no panlobular emphysema were detected by HRCT scan [19]. This contrasts with COPD, where about 1 in 3 patients displays panlobular emphysema [21]. By limiting our definition of COPD to bullae, which are the ultimate form of panlobular emphysema, we were confident that we did not inadvertently include any asthmatics. Other researchers have not reported panlobular emphysema in asthma even when it is severe or near fatal [20, 22]. Computerized emphysema scores were not used, as they cannot differentiate the type of emphysema. Computerized scores also have the drawback of failing to exclude bronchiectasis, a condition common in Saudi Arabia. Even in industrialized countries, bronchiectasis is common as an alternative or concomitant diagnosis in COPD [23, 24].

Out of 80 smoking patients in our study with salbutamol-irreversible airways obstruction (fulfilling the GOLD spirometric definition of COPD), 34 were labeled as asthmatic and 46 as COPD by their consultant. We concluded that 48 (60%) had ICS-reversible asthma, 16 (20%) had COPD, 8 (10%) had irreversible asthma and 8 (10%) had unclassified AFL. The trend for overdiagnosis of COPD was related to missing ICS-reversible asthma (poor metered dose inhaler technique and compliance) and genuine irreversible bronchial asthma. Although it is well known that misdiagnosis of asthma and COPD is common, the problem was thought to occur mostly in the elderly [1, 2]. There are no reliable data on the percentage of misdiagnosed cases. Bellia et al. [2] estimated in 2003 that every fifth elderly asthmatic is misdiagnosed as having COPD.

An earlier study that used bronchial biopsy found that out of 25 patients labeled as having COPD, 12 showed thickening of the basement membrane and displayed significant reversibility of obstruction after prednisolone [3]. This contrasts with our data, where of the 32 patients who remained obstructive after an ICS/long-acting β_2 -agonist trial, 8 had irreversible asthma (with another 5 in

the unclassified AFL group likely to be the same). Although irreversible asthma has been repeatedly reported for over 35 years, studies as recent as 2009 label it never-smokers COPD [10]. The latter study found that the great majority of the never-smokers COPD subjects (all elderly) had received a physician diagnosis of asthma or had clinical features of asthma [10]. Published reports indicate that over 20% of asthma cases become irreversible [12, 13]. This is attributed to airway remodeling in longstanding asthma [25]. Long duration of asthma, frequent exacerbations, onset in adulthood and smoking are some of the factors associated with fixed airway obstruction in asthma [12, 13, 26]. Therefore, smokers are at risk for developing not only COPD but also irreversible asthma. In a paper by Boulet et al. [27] that compared 14 patients with irreversible asthma (without significant smoking history) and a similar number of patients with COPD, DL_{CO} was normal in all irreversible asthma cases. These findings are similar to our data. However, in line with other studies, the patients with irreversible asthma in the study of Boulet et al. [27] had no significant smoking history. The present study shows that even in moderate and heavy smokers, irreversible asthma is distinguishable from COPD by displaying greater reversibility of FEV₁ (>18%) during a 1-year follow-up, normal KCO and histological features of asthma.

None of the guidelines offers a clear-cut spirometric differentiation between COPD and irreversible asthma [6, 28, 29]. Lack of reversibility is essential to the diagnosis of COPD, but the definition of reversibility varies between continents (US, British, European), resulting in wide variability in the spirometric diagnosis of COPD [30]. Single reversibility tests have consistently failed to distinguish asthma from COPD [31]. The highest sensitivity (55%) and specificity (91%) for asthma were obtained when the percentage increase in post-bronchodilator FEV₁ in relation to the predicted FEV₁ were greater than 10% [32]. However, the criteria for diagnosing asthma and COPD were based on the clinical impression of pulmonologists and were not objectively confirmed [32].

In our study, all cases of COPD had a smoking history of 50 packs/year or more. This is higher than reported in other series; the difference may be attributed to the fact that only 1 of our patients was a female, who are known to be more susceptible to COPD. Also, other series may have inadvertently included patients with irreversible asthma. Our asthmatics (whether reversible or irreversible) were younger than the COPD patients. However, age was no bar to developing any of the 3 conditions. We confirm the previous reports that worsening symptoms on

exposure to fumes or cats does not differentiate asthma and COPD [33].

The highest fluctuation of FEV₁ in 1 year (outside exacerbations) of 18% or more was associated with irreversible asthma, while all COPD patients had lower fluctuation. Reversibility can be expressed in various ways, and we selected year-long reversibility, as spirometry is known to vary longitudinally [34].

KCO distinguished fully irreversible asthma and COPD. Several studies have shown that DL_{CO} remains normal or raised in asthma, even when severe [12, 27, 35]. The situation with COPD is less clear, with conflicting results on the sensitivity and specificity of DL_{CO} [36, 37]. The discrepancy may be related to the fact that DL_{CO} remains normal in early COPD but declines considerably with advanced disease [37]. All our COPD cases were stage II or more, which could explain the uniformly low KCO. It is interesting that all the studies that used objective methods for diagnosing COPD, whether HRCT scanning or bronchial biopsy, found that DL_{CO} correlated with COPD [9, 38]. In the study of Fabbri et al. [9] on the histology of irreversible asthma and COPD, the average DL_{CO} was 85 and 65.4% predicted, respectively.

Studies going back to the 1970s used the a priori assumption that if DL_{CO} or DL_{CO}/alveolar volume is low, emphysema is diagnosed, and if normal, chronic bronchitis is diagnosed [39, 40]. However, pathological studies have demonstrated that emphysema and bronchitis can coexist and that 'pink puffer' and 'blue bloater' do not represent a major difference in the severity of emphysema [41, 42]. This may explain why in our study and in the series of Fabbri et al. [9], DL_{CO} was low in all cases of COPD even though the bronchial biopsy demonstrated clear changes of bronchitis. Moreover, the biological

markers in induced sputum are the same in both phenotypes of COPD [43].

Limitations of Our Study

The relatively small number of cases of COPD and irreversible asthma prevents us from reaching conclusive findings, especially on the role of KCO and FEV₁ fluctuation in 1 year in distinguishing the two conditions. Larger studies are needed.

Conclusions

Even in smokers, COPD as defined by the GOLD criteria includes many cases of ICS-reversible and irreversible asthma. HRCT and bronchial biopsy appear to be useful as part of the investigation of the COPD patient in selected cases. Further larger studies are needed to validate that irreversible asthma can be distinguished from genuine COPD by the novel concept of wide fluctuation of FEV₁ on follow-up for 1 year and normal KCO. The diagnosis of unclassified AFL – if widely adopted – can be useful in spurring on the search for a specific diagnosis.

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