

Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up

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Background: Both smokers and patients with asthma can experience fixed airflow obstruction, which is associated with distinctive patterns of airway pathology. The influence of fixed airflow obstruction on the prognosis of these patients is unknown.

Objective: We sought to investigate lung function decline and exacerbations in a 5-year prospective study of subjects with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease (COPD). We also sought to explore correlations between functional, pathological, and clinical features.

Methods: Patients with fixed airflow obstruction due to asthma ($n = 16$) or COPD ($n = 21$) and a control group of asthmatic patients with fully reversible airflow obstruction ($n = 15$) were followed for 5 years.

Results: The rates of decline in FEV₁ were similar in patients with fixed airflow obstruction caused by asthma (-49.7 ± 10.6 mL/y) or COPD (-51.4 ± 9.8 mL/y) and were higher than in

asthmatic patients with reversible airflow obstruction (-18.1 ± 10.1 mL/y, $P < .01$). Exacerbation rates were also higher in patients with fixed airflow obstruction caused by asthma (1.41 ± 0.26 per patient-year) or COPD (1.98 ± 0.3 per patient-year) compared with those seen in asthmatic patients with reversible airflow obstruction (0.53 ± 0.11 per patient-year, $P < .01$). Baseline exhaled nitric oxide levels and sputum eosinophil counts correlated with the FEV₁ decline in asthmatic patients with fixed airflow obstruction. By contrast, baseline sputum neutrophil counts, emphysema scores, comorbidities, and exacerbation frequency correlated directly and pulmonary diffusion capacity correlated inversely with the FEV₁ decline in patients with COPD.

Conclusion: In both patients with asthma and those with COPD, fixed airflow obstruction is associated with increased lung function decline and frequency of exacerbations. Nevertheless, the decline in lung function entails the specific pathological and clinical features of the underlying diseases. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Asthma, chronic obstructive pulmonary disease, airway inflammation, lung function, exacerbations, comorbidities, natural history

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Disclosure of potential conflict of interest: M. Contoli has received consulting fees from Chiesi Farmaceutici and has received lecture fees from Boehringer Ingelheim and AstraZeneca. S. Baraldo has received lecture fees from Boehringer Ingelheim. M. Romagnoli has received lecture fees from AstraZeneca. G. Caramori has received lecture fees from Sigma Tau, has received research support from Novartis, and has served as an expert witness for GlaxoSmithKline. M. Saetta has received lecture fees from AstraZeneca, Farmindustria, GlaxoSmithKline, Abbott Laboratories, and Boehringer Ingelheim and has received research support from GlaxoSmithKline and AstraZeneca. L. M. Fabbri has received fees for lecturing, consultancies, and advisory boards from Nycomed, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche, and Pfizer and has received research support from Chiesi Farmaceutici, Nycomed, Boehringer Ingelheim, Pfizer, Roche, and Novartis. A. Papi has received fees for lecturing, consultancies, and the advisory board from Chiesi Farmaceutici; fees for lecturing and consultancies from GlaxoSmithKline; fees for lecturing from AstraZeneca, Boehringer Ingelheim, and Merck Sharp & Dohme; and research support from AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, and Merck Sharp & Dohme. The rest of the authors have declared that they have no conflict of interest.

Received for publication June 25, 2009; revised November 17, 2009; accepted for publication January 5, 2010.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2010.01.003

Asthma and chronic obstructive pulmonary disease (COPD) are 2 distinct obstructive lung diseases with distinctive clinical presentations. Classically, asthma is characterized by airflow limitation that is reversible spontaneously or after adequate therapy,¹ whereas COPD is characterized by airflow limitation that is never fully reversible and is usually progressive, regardless of adequate therapy.² Distinctive patterns of airway inflammation and structural remodeling/derangement are constitutive parts of the pathological picture of the 2 diseases.³⁻⁵

A proportion of asthmatic patients experience a fixed airflow obstruction that persists despite optimal pharmacologic treatment.⁶ Mannino et al⁷ found that up to 30% of subjects with airflow obstruction have a history of asthma rather than COPD, but reversibility was not assessed in this epidemiologic survey. Data about the exact prevalence of fixed airflow obstruction among asthmatic patients are limited, with some studies reporting rates of about 20%⁸ and others reporting a prevalence of irreversible airflow obstruction among patients with severe asthma as high as 49%.⁹

Although asthmatic patients have been reported to have a faster lung function decline compared with that seen in healthy subjects,¹⁰ very little is known on the rate of decline in rigorously characterized aged-matched asthmatic patients and patients with

Abbreviations used

COPD: Chronic obstructive pulmonary disease
 eNO: Exhaled breath nitric oxide
 K_{CO}: Pulmonary diffusion capacity
 ROC: Receiver operating characteristic

COPD. In particular, the natural course of lung function decline in patients with fixed airflow obstruction and history of asthma without exposure to tobacco smoking is unknown. These patients deserve clinical and research attention because their disease is usually misjudged, their prognosis is unknown, and even treatment has never been properly explored. Indeed, asthmatic patients with fixed airflow obstruction are excluded from clinical trials because they cannot be labeled as having asthma or COPD.

We recently investigated a cohort of subjects with irreversible airflow obstruction and a history of asthma or COPD to evaluate whether the overlap between these 2 conditions is limited to spirometric data (ie, fixed airflow obstruction) or whether it involves also airway pathology and response to treatment.¹¹ We found 2 distinctive profiles, with the same type of irreversible airflow obstruction being associated with the pathological features typical of asthma or COPD, depending on the clinical history of the patients.¹¹ Compared with patients with COPD, asthmatic patients with a similar fixed airflow obstruction had a more intense eosinophilic inflammation in the airways, higher exhaled nitric oxide levels, lower residual volume, higher diffusing capacity, lower high-resolution computed tomographic scan emphysema scores, and greater reversibility to treatment.¹¹

In the present study we report the results of 5-year follow-up of this cohort of patients previously described cross-sectionally.¹¹ We first evaluated the rate of lung function decline and the frequency of exacerbations in patients with fixed airflow obstruction due to asthma or COPD. Second, in the search for prognostic indices, we investigated the relationships between lung function decline, airway inflammation, and clinical phenotypes in these populations.

METHODS**Study population**

The study population consisted of the previously described¹¹ cohort of patients with fixed airflow obstruction due to asthma ($n = 19$) or COPD ($n = 27$). For consistency, in the present follow-up study we maintained the same terminology: fixed airflow obstruction due to asthma or COPD. The presence of fixed airflow obstruction, both in patients with asthma and those with COPD, was defined as a postbronchodilator FEV₁/forced vital capacity ratio of less than 70% in baseline stable conditions irrespective of the magnitude of FEV₁ changes after administration of short-acting bronchodilator.^{11,12} In the original cross-sectional study (recruitment)¹¹ the presence of fixed airflow obstruction was not only evaluated after bronchodilator testing (200 μ g of albuterol), but it also persisted after a short course of systemic corticosteroids (15-day course with oral prednisone, 50 mg/d).¹¹

The inclusion criteria of patients with fixed airflow obstruction were previously described.¹¹ Briefly, asthmatic patients had a history of previous recurrent episodes of wheezing, dyspnea, chest tightness, and/or cough; had previously documented variable airflow obstruction as a bronchodilator response; and were either lifelong nonsmokers or ex-smokers with a history of less than 5 cumulative pack-years. Patients with COPD had a history of chronic respiratory symptoms (dyspnea, productive cough, or both), a history of smoking with greater than 20 cumulative pack-years, and a documented absence of reversible airflow obstruction in the past.¹¹

A third group ($n = 15$), which was not evaluated in the original cross-sectional study,¹¹ consisting of asthmatic patients with similar prebronchodilator FEV₁ but with fully reversible airflow obstruction¹ (defined as a postbronchodilator FEV₁/forced vital capacity ratio > 70%) and matched for age and prebronchodilator FEV₁ with the other 2 groups, was included in the present study for comparison of lung function decrease.

After the cross-sectional evaluation (recruitment visit¹¹), patients were asked to enter the longitudinal study, and informed consent was obtained. Those who accepted underwent the baseline visit of the longitudinal study after 2 to 3 months. In parallel, the third group (asthma with reversible airflow obstruction) was recruited and enrolled in the study.

From October 1998 to November 2005, patients belonging to these cohorts were regularly followed for 5 years and visited every 12 months. Patients were seen in stable condition and free from exacerbations for at least 3 months. They underwent physical examinations and lung function tests, exhaled breath nitric oxide (eNO) measurements, and induced sputum, as previously described.^{13,14} For diagnostic purposes, bronchial responsiveness and atopic status were evaluated at recruitment, according to standardized procedures.^{15,16}

Adverse events and exacerbations requiring medical intervention were recorded, comorbid conditions other than asthma and COPD were also assessed at each visit, and the Charlson Index was computed at baseline.¹⁷ Medical records were used to capture asthma exacerbations requiring emergency treatment or hospitalization or the need for oral steroids¹⁸⁻²⁰ and COPD exacerbations requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these.²¹⁻²³

The study conformed to the Declaration of Helsinki, the work was approved by the institutional ethics committee, and informed written consent was obtained from each subject.

Lung function

Pulmonary function tests (Biomedin Spirometer, Padova, Italy), including spirometry, total lung capacity (assessed by means of the helium dilution technique), measurement of residual volume, and pulmonary diffusion capacity (K_{CO}), were performed as previously described,^{11,13} according to published guidelines.^{24,25}

Comorbidities

The Charlson index of comorbidity, which assigns to each disease a score that is proportional to the disease-related risk of death,¹⁷ was evaluated for each patient at baseline, and it was correlated with lung function decline. In accordance with recent literature,^{26,27} the computed Charlson Index was not adjusted for age¹⁷ because the 3 groups of patients were age matched, and we did not include chronic respiratory disorders in the patients' scores because by definition all patients recruited in the study had one respiratory disorder (either asthma or COPD). At each visit, comorbidities other than asthma and COPD were recorded. A score from 0 (none) to 5 (cardiovascular disease, cancer, metabolic diseases, skeletal disorders, and others) was attributed to each patient at the end of the study.

Sputum

Induced sputum was collected and analyzed, as previously described.¹¹ Sputum plugs arising from the lower respiratory tract were selected for sputum cell counts.¹⁴

Chest high-resolution computed tomography

High-resolution computed tomographic scans of the chest were done, and the emphysema score was determined at the beginning of the study, as previously reported.^{11,28} Emphysema scores from the 31 patients of the cross-sectional study (21 with a history of COPD and 10 with a history of asthma) who completed the 5-year follow-up were available for analyses.

Statistical analysis

Lung function decline within groups was assessed by means of 1-way ANOVA. Differences at each time point from baseline were evaluated by using the *t* test. Comparison of lung function decreases between groups were performed by using 2-way ANOVA. At each time point, differences between

TABLE I. Demographics and clinical characteristics

Characteristic	Patients with fixed airflow obstruction, asthma		Patients with fixed airflow obstruction, COPD		Asthma with reversible airflow obstruction	
No. of patients	16		21		15	
Age (y)	64.5 ± 2.1		66.2 ± 1.1		63.9 ± 2.7	
Sex (M/F)	10/6		17/4		10/5	
Smoking history (pack-years)	13 NS, 3 exS (0.9 ± 0.4)		19 exS, 2 S (41.8 ± 3.8)*		13 NS, 2 exS (0.7 ± 0.2)	
Positive skin prick test response, no. (%)	15 (93)‡		1 (5)		12 (80)‡	
	Baseline	End of study	Baseline	End of study	Baseline	End of study
FEV ₁ (L)	1.63 ± 0.08	1.47 ± 0.11§	1.60 ± 0.10	1.37 ± 0.10§	1.71 ± 0.14	1.65 ± 0.13
FEV ₁ (% predicted)	54.7 ± 2.4	51.0 ± 3.1§	56.6 ± 2.2	51.9 ± 2.9§	58.9 ± 2.6	58.5 ± 2.5
FEV ₁ after bronchodilator (L)	1.88 ± 0.10	1.63 ± 0.09§	1.73 ± 0.10	1.47 ± 0.12§	2.18 ± 0.09	2.09 ± 0.12¶
FEV ₁ after bronchodilator (% predicted)	63.4 ± 2.8	56.6 ± 3.0§	61.1 ± 2.1	55.2 ± 2.8§	75.1 ± 2.1¶	74.2 ± 2.6¶
FEV ₁ /FVC ratio after bronchodilator (%)	53.2 ± 1.7	53.0 ± 1.3	51.4 ± 2.1	50.4 ± 2.3	72.1 ± 1.9¶	72.1 ± 2.0¶
ΔFEV ₁ after bronchodilator (mL)	246 ± 32	228.6 ± 29	124 ± 15	115 ± 19	461 ± 45	432 ± 38
ΔFEV ₁ after bronchodilator (% predicted)	8.4 ± 1.6	8.1 ± 1.1	4.4 ± 1.0	4.4 ± 1.2	15.8 ± 1.8¶	14.9 ± 1.4¶
RV (% predicted)	105.8 ± 5.2	111.4 ± 6.7	132.8 ± 6.3*	144.9 ± 7.1*§	102.5 ± 5.1	100.3 ± 4.9
K _{CO} (% predicted)	82.4 ± 3.5	73.8 ± 3.9§	61.1 ± 4.8†	43.5 ± 6.1§,†	85.7 ± 4.9	88.9 ± 5.2
eNO (ppb)	37.1 ± 6.7‡	33.9 ± 7.4‡	10.9 ± 1.1	9.1 ± 1.3	28 ± 9.1‡	21 ± 7.9‡
Inhaled steroids, no. (%)	16 (100)	16 (100)	17 (80)	19 (90)	12 (80)	15 (100)
Systemic steroids, no. (%)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Inhaled long-acting β ₂ -agonist, no. (%)	15 (94)	16 (100)	21 (100)	21 (100)	13 (87)	14 (93)
Inhaled short-acting antimuscarinic, no. (%)	0 (0)	0 (0)	7 (33)*	1 (5)§	0 (0)	0 (0)
Inhaled long-acting antimuscarinic, no. (%)	0 (0)	0 (0)	0 (0)	6 (28)*,§	0 (0)	0 (0)

exS, Ex-smoker; F, female; FVC, forced vital capacity; K_{CO}, carbon monoxide transfer coefficient; M, male; NS, nonsmoker; RV, residual volume; S, smoker.

**P* < .05 versus patients with fixed airflow obstruction due to asthma and versus patients with asthma with reversible airflow obstruction.

†*P* < .01 versus patients with fixed airflow obstruction due to asthma and versus patients with asthma with reversible airflow obstruction.

‡*P* < .05 versus patients with fixed airflow obstruction due to COPD.

§*P* < .05 versus baseline.

||*P* < .05 and ¶*P* < .01 versus patients with fixed airflow obstruction due to COPD or asthma.

groups were calculated by using the unpaired *t* test. Changes at the end of the study versus baseline were evaluated by using paired *t* tests or Wilcoxon signed-rank tests or the χ^2 test, as appropriate. Comparisons among groups were evaluated by using ANOVA and the Student *t* test or Kruskal-Wallis and Mann-Whitney test or the χ^2 test, as appropriate.

The Bonferroni correction was used for multiple comparisons. Linear regression analysis was used when appropriate, and the Pearson test was used to investigate correlations. Receiver operating characteristic (ROC) curve analysis was performed for inflammatory biomarkers to define their capability to predict (predictive value) lung function decrease and other clinically relevant outcomes. The area under the ROC curves was determined, and a value of greater than 0.80 was considered a good discrimination.²⁹ ROC curve analysis allowed (sensitivity vs 1 minus specificity) selection of the best discriminating cutoff point of each variable.

P values of less than .05 were considered significant. In the case of multiple comparisons, the reported *P* values refer to analyses adjusted by using the Bonferroni correction. All analyses were performed with GraphPad Prism 5.0 for Windows (GraphPad Software, Inc, La Jolla, Calif).

RESULTS

Of the 46 patients with fixed airflow obstruction constituting the population of the original cross-sectional study,¹¹ 80% completed the 5-year follow-up (21 with a history of COPD and 16 with a history of asthma). Nine patients did not complete the

study for the following reasons: 4 died (3 patients with a history of COPD and 1 with a history of asthma, *P* > .5), and 5 patients (3 patients with a history of COPD and 2 with a history of asthma, *P* > .5) refused consent.

Demographic and baseline characteristics of the patients participating in the longitudinal study are summarized in Table I. No difference was found in demographic, functional, and inflammatory parameters between patients who completed the 5-year follow-up and those of the original cross-sectional cohort.¹¹ The 3 groups of patients were matched for age, sex, and prebronchodilator airflow obstruction. Asthmatic patients with fixed airflow obstruction and patients with COPD had similar postbronchodilator FEV₁. Also, the 3 groups had similar exposure to inhaled corticosteroids and long-acting β₂-agonists.

A proportion of patients with COPD (*n* = 6; 28%) started a regular treatment with the antimuscarinic tiotropium during the follow-up period. These patients were previously treated with short-acting antimuscarinic agents (Table I). We did not find any specific differences between these 6 patients and the remaining 15 patients of the COPD group in any of the outcomes explored.

Lung function changes over 5 years of follow-up

Postbronchodilator FEV₁. Overall, the population with fixed airflow obstruction had a progressive postbronchodilator

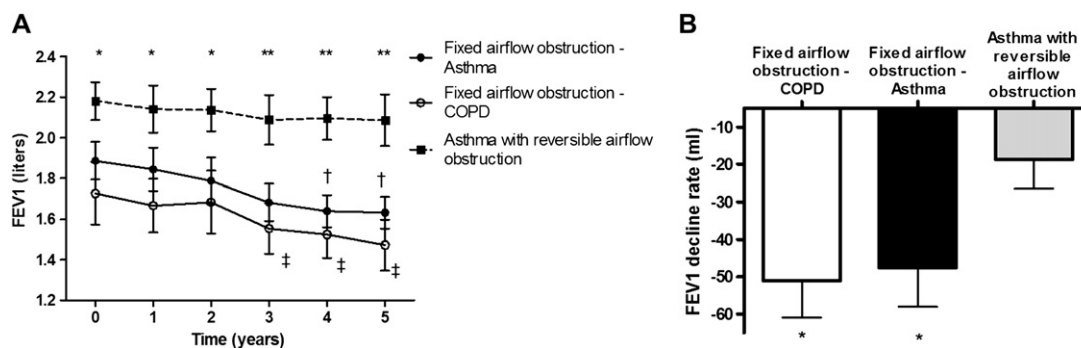


FIG 1. FEV₁ decline rates over 5 years in patients with fixed airflow obstruction due to asthma or COPD. **A**, Changes in postbronchodilator FEV₁ over the 5-year follow-up. * $P < .05$ versus patients with fixed airflow obstruction due to asthma or COPD at the same time point. ** $P < .01$ versus patients with fixed airflow obstruction due to asthma or COPD at the same time point. † $P < .05$ versus baseline. ‡ $P < .05$ versus baseline. Error bars indicate SEMs. **B**, Mean postbronchodilator FEV₁ decline per year. * $P < .01$ versus asthmatic patients with fully reversible airflow obstruction. Error bars indicate SEMs.

FEV₁ decline over time ($P < .001$, ANOVA). Mean postbronchodilator FEV₁ decline was -50.1 ± 6.8 mL/y, corresponding to a decline rate of $-1.28\% \pm 0.18\%$ of predicted value per year.

Postbronchodilator FEV₁ declined progressively in patients with fixed airflow obstruction caused by asthma ($P < .001$, ANOVA; Fig 1, A, and Table I). Mean decrease was -49.7 ± 10.6 mL/y (Fig 1, B), corresponding to a decrease rate of $-1.37\% \pm 0.28\%$ of predicted value per year.

In patients with fixed airflow obstruction due to COPD, postbronchodilator FEV₁ declined progressively over time ($P < .001$, ANOVA; Fig 1, A, and Table I). Mean postbronchodilator FEV₁ decline was -51.4 ± 9.8 mL/y (Fig 1, B), corresponding to a decline rate of $-1.19\% \pm 0.24\%$ of predicted value per year.

In asthmatic patients with fully reversible airflow obstruction, postbronchodilator FEV₁ values did not change significantly throughout the study (Fig 1, A). None of the patients with fully reversible airflow obstruction developed fixed airflow obstruction during the 5-year follow-up.

The rate of postbronchodilator FEV₁ decline was similar in patients with fixed airflow obstruction due to asthma or COPD ($P = .71$), and it was steeper compared with that seen in asthmatic patients with fully reversible airflow obstruction (-18.1 ± 10.1 mL/y, $P < .01$; Fig 1, B).

Other lung function measurements. At the end of the 5-year follow-up, residual volume was not significantly changed from baseline in patients with fixed airflow obstruction caused by asthma, whereas it was significantly increased in those with a history of COPD (Table I). As compared with baseline, the K_{CO} value was significantly reduced after 5 years in patients with fixed airflow obstruction due to either asthma or COPD (Table I). The reduction of K_{CO} percent predicted was significantly lower in asthmatic patients with fixed airflow obstruction ($-8.6\% \pm 2.1\%$ of predicted value) compared with patients with COPD ($-17.63\% \pm 3.5\%$ of predicted value, $P < .01$). During the 5-year study, the control group of asthmatic patients with fully reversible airflow obstruction showed no change in residual volume and K_{CO} (Table I).

Relationships between the rates of FEV₁ decline, lung function measurements, and emphysema scores in patients with fixed airflow obstruction

Among patients with fixed airflow obstruction due to asthma, but not among those with fixed airflow obstruction due to COPD,

reversibility to bronchodilator at baseline negatively correlated with FEV₁ decline over 5 years ($P < .05$, $r = -0.54$). In patients with fixed airflow obstruction due to COPD, but not in patients with fixed airflow obstruction due to asthma, there was an inverse correlation between baseline K_{CO} values (percent predicted) and FEV₁ decline rate ($P < .01$, $r = -0.51$), whereas the initial emphysema score correlated positively with the rate of FEV₁ decline over 5 years ($P < .05$, $r = 0.47$).

The exclusion from the analyses of the 4 asthmatic patients of this group with higher reversibility (ie, response to short-acting β_2 -agonist bronchodilators >200 mL and $>12\%$ of predicted value) did not affect any of the results described in this study.

Airway inflammation: 5-year follow-up

Sputum total cell counts did not significantly change during the 5-year follow-up in patients with fixed airflow obstruction due to asthma or COPD (Table II). Sputum eosinophil counts were significantly higher in patients with fixed airflow obstruction due to asthma than in patients with fixed airflow obstruction due to COPD both at baseline and at the end of the study (Table II). Conversely, sputum neutrophil counts were higher in patients with fixed airflow obstruction due to COPD both at baseline and at the end of the 5-year follow-up (Table II).

In patients with fixed airflow obstruction due to asthma, the percentage of sputum eosinophils decreased over time ($P < .01$, ANOVA), and the reduction was significant from 3 years onward.

Relationships between the rates of FEV₁ decline and baseline airway inflammation in patients with fixed airflow obstruction

Patients with fixed airflow obstruction due to asthma, but not those with fixed airflow obstruction due to COPD, showed a positive correlation between the rates of decrease in FEV₁ and both the percentage of baseline sputum eosinophils ($P < .05$, $r = 0.53$; Fig 2, A) and baseline eNO levels ($P < .05$, $r = 0.55$). Conversely, the percentage of sputum neutrophils at baseline positively correlated with the rates of FEV₁ decline in patients with fixed airflow obstruction due to COPD ($P < .05$, $r = 0.49$; Fig 2, B) but not due to asthma.

The percentage of sputum eosinophils in patients with fixed airflow obstruction due to asthma and the percentage of sputum

TABLE II. Sputum differential cell counts in patients with fixed airflow obstruction

	Patients with fixed airflow obstruction, asthma		Patients with fixed airflow obstruction, COPD	
	Baseline	End of study	Baseline	End of study
No. of cells (10^5 cells/mL)	8 (4–9)	8 (5–12)	8 (5.6–13)	7.4 (4.5–10.6)
Macrophages (%)	24 (9.5–32.7)	23.8 (10.1–31.4)	21 (16.5–26.7)	22.5 (15–36)
Neutrophils (%)	70.0 (52.2–79)	68 (65–79.4)	79 (70.5–82)*	76 (64–82.2)†
Eosinophils (%)	9.5 (2.5–15)‡	5.3 (2–6.7)§,	0.5 (0–1.9)	0 (0–2)
Lymphocytes (%)	0.5 (0–1)	0 (0–1)	0.5 (0–0.5)	0 (0–0)

Data are expressed as medians (interquartile ranges).

* $P < .05$ versus patients with fixed airflow obstruction due to asthma at baseline.

† $P < .05$ versus patients with fixed airflow obstruction due to asthma at the end of the study.

‡ $P < .01$ versus patients with fixed airflow obstruction due to COPD at baseline.

§ $P < .01$ versus patients with fixed airflow obstruction due to COPD at the end of the study.

|| $P < .05$ versus baseline.

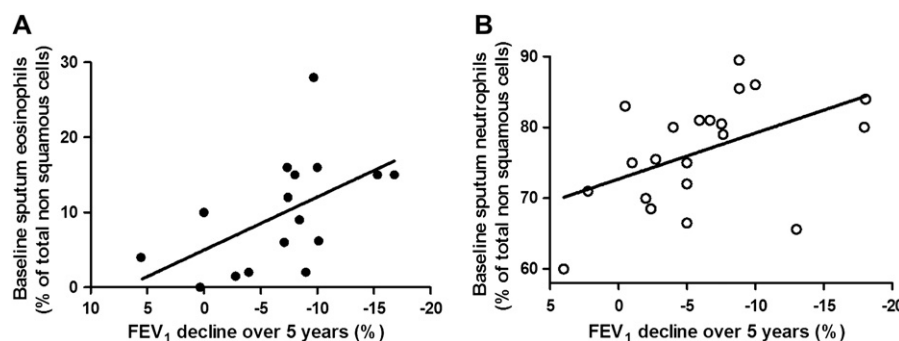


FIG 2. Correlations between rates of FEV₁ decline and markers of airway inflammation. Correlations between rates of FEV₁ decline (percent predicted) over 5 years and the percentage of sputum eosinophils at baseline in patients with fixed airflow obstruction due to asthma ($P < .05$, $r = 0.53$; **A**) and the percentage of sputum neutrophils at baseline in patients with fixed airflow obstruction due to COPD ($P < .05$, $r = 0.49$; **B**) are shown.

neutrophils in patients with COPD were good predictors of accelerated lung function decrease (values of the area under the ROC curves, 0.81 and 0.83, respectively). In asthmatic patients with fixed airflow obstruction, a percentage of sputum eosinophils greater than 6.1% (best cutoff point with a sensitivity of 0.88 and a specificity of 0.71) significantly predicts a decrease in lung function greater than the median value of the group (-1.54% predicted per year), whereas in patients with COPD, a percentage of sputum neutrophils greater than 77.3% (best cutoff point with a sensitivity of 0.80 and a specificity of 0.81) significantly predicts a decrease in lung function greater than the median value of the group (-1.00% predicted per year).

Exacerbations: 5-year follow-up

During the 5-year study, a total of 361 exacerbations requiring medical intervention were recorded, of which 15 (4.15%) required hospitalization. The mean number of exacerbations per patient-year was no different between patients with fixed airflow obstruction due to asthma (1.41 ± 0.26) or COPD (1.98 ± 0.3), and it was significantly higher compared with that seen in the asthmatic patients with reversible airflow obstruction (0.53 ± 0.11 , $P < .01$). The percentage of exacerbations requiring hospitalization tended to be higher in patients with fixed airflow obstruction due to COPD compared with that seen in patients with fixed airflow obstruction due to asthma (6.2% vs 1.7% of total

exacerbations, respectively; $P = .07$). None of the exacerbations occurring in asthmatic patients with reversible airflow obstruction required hospitalization.

A positive correlation was found between the percentage of sputum eosinophils at baseline and the frequency of exacerbation ($P < .01$, $r = 0.79$) in patients with fixed airflow obstruction due to asthma (Fig 3, A). By contrast, in patients with fixed airflow obstruction due to COPD, the frequency of exacerbations was positively correlated with baseline sputum neutrophil counts ($P < .05$, $r = 0.48$; Fig 3, B). In patients with COPD, the frequency of exacerbations was also positively correlated with the FEV₁ decline rate ($P < .05$, $r = .53$) and with patients' self-reported comorbidities at baseline, as assessed by means of the Charlson Index ($P < .05$, $r = 0.47$).

The percentage of sputum eosinophils in patients with fixed airflow obstruction due to asthma and the percentage of sputum neutrophils in patients with COPD were good predictors of increased frequency of exacerbations (values of the area under the ROC curves, 0.86 and 0.84, respectively). In asthmatic patients with fixed airflow obstruction, a percentage of sputum eosinophils greater than 9.5% (best cutoff point with a sensitivity of 0.87 and a specificity of 0.87) significantly predicts increased frequency of exacerbations greater than the median value of the group (1.1 exacerbation per year), whereas in patients with COPD, a percentage of sputum neutrophils greater than 79.5% (best cutoff

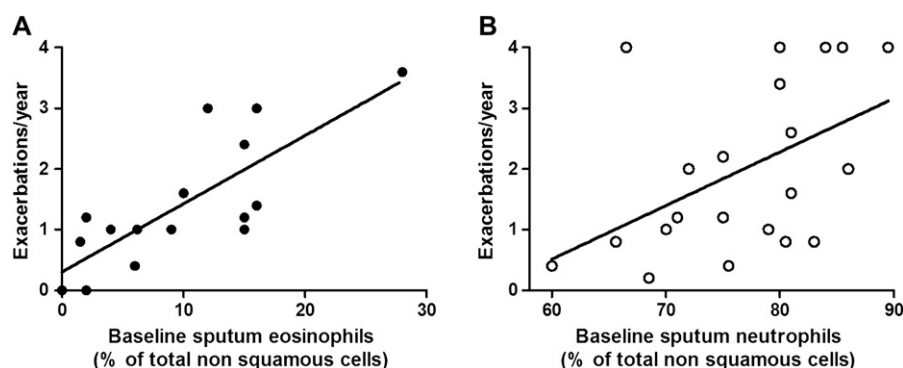


FIG 3. Correlations between exacerbation frequency and markers of airway inflammation. Correlations between the mean number of exacerbations per patient per year and the percentage of sputum eosinophils at baseline in patients with fixed airflow obstruction due to asthma ($P < .01$, $r = 0.79$; **A**) and the percentage of sputum neutrophils at baseline in patients with fixed airflow obstruction due to COPD ($P < .05$, $r = 0.48$; **B**) are shown.

point with a sensitivity of 0.72 and a specificity of 0.80) predicts a frequency of exacerbation greater than the median value of the group (1.6 exacerbations per year).

Comorbidities: 5-year follow-up

At baseline, the Charlson index was significantly higher in patients with COPD (2.23 ± 0.4 , $P < .01$) than in the 2 groups of asthmatic patients (0.81 ± 0.20 and 0.73 ± 0.22 in asthmatic subjects with and without fixed airflow obstruction, respectively). At the end of the study, the number of coexistent illnesses was higher in patients with COPD (1.95 ± 0.26 , $P < .01$) than in the 2 groups of asthmatic patients (0.85 ± 0.16 and 0.70 ± 0.16 in asthmatic subjects with and without fixed airflow obstruction, respectively). In the COPD group only, a positive correlation was found between the baseline Charlson Index and the decline in FEV₁ ($P < .001$, $r = 0.68$). Moreover, among patients with COPD, a positive correlation was found between the percentage of neutrophils in sputum at baseline and the number of comorbidities at the end of the study ($P < .05$, $r = 0.54$).

DISCUSSION

This is a 5-year follow-up study conducted in a cohort of patients previously described cross-sectionally as having fixed airflow obstruction with either a history of asthma or COPD. We found that patients with fixed airflow obstruction due to either COPD or asthma had a greater postbronchodilator FEV₁ decline compared with that seen in asthmatic patients with reversible airflow obstruction. The rate of lung function decline was similar in patients with fixed airflow obstruction due to asthma or COPD. Similarly, the frequency of exacerbations was higher in patients with fixed airflow obstruction due to asthma or COPD than in asthmatic subjects with reversible airflow obstruction.

Previous studies have shown that asthmatic patients have a faster decline in lung function compared with healthy subjects,^{10,30} and the excess decline that characterizes COPD has been extensively described.³¹⁻³³ However, no study has previously compared lung function decline in fully characterized patients with a clinical history of either asthma or COPD who share a similar degree of fixed airflow obstruction. This study indicates that the presence of a fixed airflow obstruction might be a key prognostic determinant. Indeed, age-matched patients with

reversible airway obstruction have a slower rate of lung function decline, which is close to previously reported values,¹⁰ whereas persistent airflow obstruction accelerated lung function decline irrespective of the underlying disease. Whether a similar accelerated lung function decline characterizes fixed airflow obstruction also in younger asthmatic patients needs to be evaluated in specific studies.

Interestingly, in a classical epidemiologic study, Burrows et al³⁴ reported that among patients with airflow obstruction, those self-referred as “chronic asthmatic bronchitics” had a lower FEV₁ decline compared with that seen in smokers with a similar airflow obstruction and no history of asthma. There are obvious differences between the Burrows et al study and the present study (eg, self-reported diagnosis vs careful clinical characterization; the enrollment diagnostic criteria of “chronic asthmatic bronchitis” vs asthma with fixed airflow obstruction persisting after bronchodilators and a short course of systemic corticosteroids) that might explain the discrepancies.

Extensive characterization of our population at baseline¹¹ allowed us to recognize that the development of fixed airflow limitation in asthmatic patients modifies the rate of lung function decline, which becomes similar to that of COPD. However, in patients with fixed airflow obstruction due to asthma, but not in patients with fixed airflow obstruction due to COPD, there is a direct relationship between the rate of decline and some of the markers of the airway inflammation typical of asthma, such as sputum eosinophil counts and eNO levels. By contrast, only in patients with COPD are some features of the disease (eg, increased sputum neutrophil counts and emphysema scores and impaired diffusion capacity) related to the lung function decline rate. Thus when fixed airflow obstruction is present, the accelerated lung function decline is associated with specific characteristics of the underlying disease. Notably, none of these relationships could be identified when we considered the population of patients with fixed airflow obstruction as a whole. This observation is particularly relevant in the design and interpretation of epidemiologic studies because important clinical outcomes could be missed when relying on spirometric patterns only for patient selection in the absence of an accurate clinical history.

In previous studies it has been reported that bronchodilator reversibility is a potential predictor of accelerated FEV₁ decline in patients with asthma.^{8,35} Here we found an inverse relationship:

the higher the reversibility to bronchodilator, the lower the rate of decline. Our report evaluated only asthmatic patients with fixed airflow obstruction, which might be responsible for the difference with previous studies, further emphasizing the concept that it is the presence of irreversible airflow obstruction that influences the rate of decline in this population.

In our study residual volume significantly increased only in patients with COPD. In addition, the decrease of K_{CO} over 5 years was significantly higher in patients with COPD than that observed in asthmatic patients with fixed airflow obstruction. These data, together with the observations that emphysema score and K_{CO} impairment positively correlated with lung function decline only in patients with COPD, suggest that parenchymal destruction is not just an aspect of COPD pathogenesis but also contributes to COPD progression, whereas it has only marginal relevance in the pathogenesis and progression of asthma, even in the presence of fixed airflow obstruction.

There is evidence in patients with COPD that airway neutrophilia progressively increases with worsening of pulmonary function.^{36,37} Intriguingly, in our study the percentage of sputum neutrophils in patients with COPD was also related to the number of exacerbations, and in line with recent studies,³⁸ we found that the higher the exacerbation rate, the faster the decline in FEV_1 . Taken together, these observations suggest that there is a close interplay between exacerbations, neutrophil counts, and lung function decline in patients with COPD: patients experiencing frequent exacerbations have repeated bursts of airway neutrophilia and are more prone to a rapid decline in lung function. Conversely, in patients with fixed airflow obstruction due to asthma, we found a positive correlation between sputum eosinophil counts at baseline and the frequency of exacerbation. We also found that sputum inflammatory cell counts (eosinophils in patients with asthma and neutrophils in patients with COPD) could have predictive value on exacerbation rate and lung function decline. However, given the limited number of patients included in our cohort, these data need to be confirmed in a larger population. The persistence of eosinophilic inflammation despite regular inhaled corticosteroid treatment suggests that asthmatic patients with fixed airflow obstruction are refractory to inhaled corticosteroid treatment. Such a poor response leads to persistent inflammation, which in turn might contribute to the acceleration in lung function decline in asthmatic subjects with fixed airflow obstruction.⁹ It is also possible that fixed airflow obstruction develops in steroid-refractory patients through uncontrolled airway inflammation leading to structural changes and persistent airflow limitation. Moreover, in line with our observation, a recent study showed that eNO levels could predict lung function decline in patients with clinical difficult-to-treat asthma.³⁹ Contrary to recent studies in patients with mild-to-moderate asthma,^{40,41} we found no relationships between exacerbation frequency and lung function decline in our asthmatic patients. This might be due to differences in the populations but also to the limited number of patients considered in our explorative study. Our study has only begun to fulfill a relevant medical need in respiratory medicine: the lack of information on a relevant proportion of the asthmatic population that has been neglected from clinical investigations. This is the first report of a cohort of well-characterized patients with fixed airflow obstructions due to asthma or COPD in which a 5-year follow-up has been performed. The careful characterization of the original cohort of patients,¹¹ which we followed over 5 years, is one of the major strengths of the study, which allowed us to

unmask the importance of fixed airflow obstruction in a prognostic perspective that goes beyond the horizon of COPD.

Compared with age-matched healthy subjects, patients with COPD are more frequently affected by comorbidities^{42,43} that contribute to morbidity severity and mortality.^{27,44} We found that patients with COPD have a higher prevalence of comorbid conditions than age-matched asthmatic subjects, even when they share a similar fixed airflow obstruction. The higher prevalence of chronic comorbid conditions in patients with COPD could be related to the smoking habits of these subjects.⁴⁵

In conclusion, this study shows that patients with fixed airflow obstruction caused by either asthma or COPD have an accelerated lung function decline and an increased frequency of exacerbations compared with those seen in asthmatic patients fully reversible to bronchodilator. However, in subjects with fixed airflow obstruction, both lung function impairment and exacerbation frequency are associated with pathogenetic substrates, which are specific for the underlying disease (asthma vs COPD). Therapeutic strategies should be addressed to different cellular targets, pathogenetic aspects, or both in the 2 diseases.

Clinical implications: Fixed airflow obstruction leads to increased lung function decline and frequency of severe exacerbations in both patients with asthma and those with COPD. Distinctive clinical and inflammatory markers predict the degree of lung function decline.

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