COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

informa healthcare

COPD, 10:55–61, 2013
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2012.727920

ORIGINAL RESEARCH

The Rapid FEV_1 Decline in Chronic Obstructive Pulmonary Disease Is Associated with Predominant Emphysema: A Longitudinal Study

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Abstract

Background: **Early identification of patients with COPD and prone to more rapid decline in lung function is of particular interest from both a prognostic and therapeutic point of view. The aim of this study was to identify the clinical, functional and imaging characteristics associated with the rapid FEV_1 decline in COPD.** ***Methods:*** **Between 2001 and 2005, 131 outpatients with moderate COPD in stable condition under maximum inhaled therapy underwent clinical interview, pulmonary function tests and HRCT imaging of the chest and were followed for at least 3 years.** ***Results:*** **Twenty-six percent of patients had emphysema detected visually using HRCT. The FEV_1 decline was 42 ± 66 mL/y in the total sample, 88 ± 76 mL/y among rapid decliners and 6 ± 54 mL/y among the other patients. In the univariable analysis, the decline of FEV_1 was positively associated with pack-years ($p < 0.05$), emphysema at HRCT ($p < 0.001$), RV ($p < 0.05$), FRC ($p < 0.05$), FEV_1 ($p < 0.01$) at baseline and with number of hospitalizations per year ($p < 0.05$) during the follow-up. Using multivariable analysis, the presence of emphysema proved to be an independent prognostic factor of rapid decline ($p = 0.001$). When emphysema was replaced by RV, the model still remained significant.** ***Conclusions*****: The rapid decline in lung function may be identified by the presence of emphysema at HRCT or increased RV in patients with a long smoking history.**

Abbreviations

CI	confidence intervals
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study (ECLIPSE study)
FEV_1	forced expiratory volume in 1 one second
FRC	functional residual capacity
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	high resolution computed tomography
OR	Odds ratios
RV	residual volume
TGV	thoracic gas volume
TLC	total lung capacity
UPLIFT	Understanding Potential Long-Term Impacts on Function with Tiotropium study (UPLIFT study)

Keywords: Lung function decline, Hyperinflation, Computed tomography, Follow-up studies

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Introduction

The classical approach to chronic obstructive pulmonary disease (COPD) has encompassed different disorders in a unique entity under a variety of imprecise definitions and diagnostic criteria. The current definition of COPD is based on the presence of airflow obstruction that is not completely

reversible with inhaled bronchodilators, irrespective of the presence of symptoms or the existence of emphysematous changes in the lungs (1). Yet, clinical, functional and radiological presentation varies greatly from patient to patient despite having a similar degree of airflow obstruction (2,3). A major practical problem with disregarding the heterogeneity of COPD is that not all individual patients may respond to a given treatment and, therefore, the opportunity to optimise therapy may be missed. The uncritical inclusion of COPD patients in the recent, large therapeutic trials could have biased, at least in part, the results on mortality and reversibility of the disease process (3,4).

Several methods have attempted to address the issues of disease heterogeneity and cluster analysis shows promise in identifying disease subtypes based on clinical, physiological and radiological characteristics (5–8). However, caution is warranted when clustering patients with similar symptoms and clinical manifestations. From a clinical and patient-centered perspective, a COPD phenotype should be able to classify patients into distinct subgroups that provide prognostic information and allow us to better determine appropriate therapy that alters clinically meaningful outcomes. It is well known that some patients are prone to more rapid decline in lung function (rapid decliners) than others (slow decliners).

Rapid decline in forced expiratory volume in 1 second (FEV_1) is predictive of morbidity, mortality and hospitalization rates (9), and has also been linked to distinct plasma biomarker signatures (10). The early identification of patients with rapid decline in FEV_1 should be of particular interest from both the prognostic and therapeutic point of view. The aim of the study was to identify the baseline characteristics associated with the rapid decline in FEV_1 in a well-defined cohort of outpatients with moderate COPD recruited at the time of their first visit at our outpatient clinic and followed for at least 3 years.

Methods

Patients

Between 2001 and 2005, 490 patients presenting with suspected COPD for the first time at the outpatient clinic of the Division of Respiratory Diseases- Fondazione IRCCS Policlinico "San Matteo" were diagnosed with moderate to very severe COPD and received triple or double inhalation therapy; that is, inhaled corticosteroid (fluticasone or budesonide) with long-acting B_2-agonist (salmeterol or formoterol) + long-acting antimuscarinic (tiotropium) or with only one long-acting bronchodilator.

Study design

After 3 months, patients confirmed to be in stable condition were re-evaluated and underwent extensive pulmonary function testing; 131 of them were diagnosed with moderate COPD (post-bronchodilator FEV_1/ forced vital capacity (FVC) <70% and FEV_1 between 80% and 50% of predicted value) (1) and agreed to participate to an observation study of at least three years. The patients agreed to undergo chest high resolution computed tomography (HRCT) and to be evaluated when in stable condition at least once a year for the scheduled follow-up. During the follow-up they maintained the same inhalation therapy and exacerbations were managed by their usual physicians according to standard medical practices. All participants gave written informed consent prior to their inclusion in the study and the Fondazione IRCCS Policlinico "San Matteo" ethics committee approved the study.

Clinical evaluation

The clinical examinations were performed by three physicians involved in the study. During the interview patient answered questions regarding: smoking status, pack-year history, environmental and occupational exposure, respiratory infections during childhood, self-reported major co-morbidities (congestive heart failure, coronary artery disease, depression, osteoporosis, anaemia, diabetes mellitus), previous diagnoses, previous treatments, acute previous and follow-up exacerbations requiring or not hospitalisation, presence of chronic respiratory symptoms. We excluded patients with asthma from the study; the presence of asthma was determined on the basis of a physician's diagnosis or self-reported history, symptoms and asthma treatment.

Other exclusion criteria were as follows: uncontrolled co-morbidities likely to affect mortality within 3 years, such as malignant disorders or severe cardiovascular disease; history of bronchiectasies; extensive residual radiological signs of pulmonary tuberculosis or of other previous infectious or non-infectious cardiopulmonary diseases; problems that could prevent effective collaboration and communication. Self-reported exacerbations during the previous three years before the study begun were classified as few exacerbations (≤2) or frequent exacerbations (>2), while those during the follow-up were classified as requiring or not hospitalisation.

Pulmonary functional evaluation

Spirometry (Autobox V6200 and Vmax 22 system; Sensormedics Corp; Yorba Linda, California) was performed following the American Thoracic Society recommendations at the first visit, at the second visit within 3 months and every year until the end of follow-up (11). FVC and FEV_1 were measured at baseline and 15 minutes after salbutamol administration (400 mcg). The drug was given by metered dose inhaler through a spacer device. An increase in FEV_1 and/or FVC that is both greater than 200 ml and 12% above the pre-bronchodilator FEV_1 was considered significant. Thoracic gas volume was measured at baseline by body plethysmography and total lung capacity (TLC), residual volume (RV), and functional residual capacity (FRC) were obtained.

Predicted values for spirometry and lung volumes were from Quanjer et al. (12).

CT imaging evaluation

At the beginning of the follow-up a spiral HRCT imaging was performed at different radiology services because it was logistically difficult to perform all the HRCT scanning at our center. HRCT scans were acquired using multi-detector computed tomography scanners (at least 16 detector channels). Volumetric HRCT acquisitions were obtained on full inspiration. Image reconstruction utilized sub-millimeter slice thickness, with smooth and edge-enhancing algorithms. We centralized HRCT scan review to insure both consistency and accuracy in visual assessment of emphysema. Separately, two expert radiologists read the scans unaware of the clinical data and compared results; in case of discrepancy, the decision was taken by a consensus reading with a third radiologist. They utilized the scale proposed by Goddard et al. (13) to rate the extent of emphysema for each lung field on each scan. In particular the score zero and 1 represented respectively absence of emphysema and less than 25% of lung parenchyma showing emphysema changes and the score 2, 3, 4 represented emphysema involvement greater than 25% up to total involvement.

Table 1. Patient baseline characteristics

Variables	
Age, *years*	69.7 ± 7.6
Gender	
Male, *n. (%)*	112 (85.5%)
Female, *n. (%)*	19 (14.5%)
Body mass index, kg/m^2	26.8 ± 4.2
Smoking history	
Current, *n. (%)*	22 (17.2%)
Former, *n. (%)*	97 (76.6%)
Never, *n. (%)*	8 (6.3%)
pack-years, *median n. (25th-75th)*	47 (30–61)
Patients with emphysema, *n. (%)*	34 (26.0%)
Patients with major co-morbidities, *n. (%)*	33 (25.2%)
Post-bronchodilator pulmonary function data	
FEV_1, *L (% pred.)*	1.81 ± 0.49 (69 ± 14%)
FEV_1/FVC, *%*	59 ± 9%
FRC, *L (% pred.)*	4.1 ± 0.9 (123 ± 24%)
TLC, *L (% pred.)*	6.45 ± 1.13 (105 ± 16%)
RV, *L (% pred.)*	3.4 ± 0.9 (129 ± 32%)

Values are mean ± SD unless otherwise indicated.

Statistics

Data were described as the mean and standard deviation or median and 25^{th}–75^{th} percentiles if continuous and as counts and % if categorical. For the purpose of the present analysis, we considered emphysema present when the emphysema score was greater than 1 and absent when it was zero or 1. The individual decline in FEV_1 during the follow-up was obtained by linear regression of all the FEV_1 values measured during the follow up. For the purpose of the analysis, the decline in FEV_1 was dicotomized at the 50^{th} percentile of the distribution of individual regression coefficient: patients with values greater than the median value were defined as rapid decliners.

The change in FEV_1 was computed as the difference between FEV_1 measured at the beginning and at the end of the follow-up, divided by the duration of the follow-up (expressed in mL/y). Presenting characteristics were compared between rapid decliners and non-rapid decliners with logistic model. Odds ratios (OR) and their 95% confidence intervals (95%CI) were estimated. Non-collinear variables showing a p-value <0.05 at the univariable analysis were included in a multivariable model. A test for goodness of fit was performed. All tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Table 1 shows the subjects' baseline characteristics. All 131 subjects had moderate COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD stage II) and some of them had lung hyperinflation (i.e., an increase in FRC), gas trapping (i.e., an increase in RV). Thirty-two percent of the patients demonstrated reversibility of airflow obstruction. According to the qualitative HRCT scan analysis, 26.0% of the patients were judged to have a non-trivial emphysema. Thirty-three patients reported major co-morbidities; in particular 25.2% reported cardiovascular co-morbidities.

The large majority of the 131 subjects were former (76.4%) or current smokers (17.3%); 31.3% of the patients reported childhood respiratory diseases or passive smoking or occupational exposure. Ninety-five percent of the patients reported chronic respiratory symptoms: 27.2% reported only dyspnoea at rest or during exercise, 42.4% only chronic cough and/or phlegm and 30.4% both dyspnoea and chronic cough and/or phlegm. At baseline almost half of the patients did not report COPD exacerbations during their life while 26.0% reported frequent and 24.4% reported only few exacerbations.

The mean duration of follow-up was 4.3 ± 1.3 years. During the study, 70.9% of the patients were receiving triple and the remainder double therapy. Good adherence was self reported by 92.3% of the patients. The median number of exacerbations was 0.3 (25^{th}–75^{th}, 0.0–0.7) per year; the mean number of those requiring hospitalization was 0.0 (25^{th}–75^{th}, 0.0–1.0) per year. The mean number of exacerbations per year was significantly higher in patients with previous frequent exacerbations ($p < 0.0001$). The median value of individual regression coefficient of decline in FEV_1 was -0.06 (25^{th}–75^{th}, –0.18–0.03). The mean and the median FEV_1 decline were 42±66 mL/y and 40 mL/y, respectively. The mean

FEV_1 decline was 88 ± 76 mL/y among rapid decliners, and it was 6 ± 54 mL/y among the other patients.

In the univariable analysis, rapid decliners were positively associated with the number of smoking pack-years ($p < 0.05$), presence of emphysema ($p < 0.001$), FEV_1 percent predicted ($p < 0.05$) and absolute value ($p < 0.05$), FRC percent predicted ($p < 0.01$) and absolute value ($p < 0.05$), RV absolute value ($p < 0.05$) at baseline and number of exacerbations requiring hospitalizations per year ($p < 0.05$) during the follow-up (Table 2).

In the multivariable analysis, the presence of emphysema proved to be an independent prognostic factor of rapid decline in FEV_1, with a consistent increase in risk of being a rapid decliner, after adjustment for smoking, duration of smoking, chronic cough and phlegm without dyspnoea; none of these were significantly associated with FEV_1 decline. When the presence of emphysema was replaced by mean RV, the model still remained significant (Table 3, models 1 and 2, respectively).

Table 2. Univariable association between FEV_1 decline and different anthropometric, clinical and functional variables

Characteristic	Rapid decliner	Non-rapid decliner	OR (95%CI)	*p*-Value
Patients, *n.*	65	66		
Age, *years, median (25th–75th)*	72 (66–75)	69 (64–76)	1.44 (0.73–2.86)	0.30
Gender: male, *n. (%)*	58 (89.2)	54 (81.8)	0.69 (0.26–1.84)	0.46
Body mass index, *kg/m², median (25th–75th)*	26.7 (23.5–29.1)	26.5 (24.0–30.3)	1.13 (0.57–2.23)	0.73
Smoking history, *n (%)*				0.24
Never	2 (3.0)	6 (9.7)		
Current	13 (19.7)	9 (14.5)	4.33 (0.71–26.53) 3.26 (0.63–16.93)	
Former	51 (77.3)	47 (75.8)		
Pack-years, *median (25th–75th)*	50 (37–69)	39 (28–58)		**0.029**
Duration of smoking, *years, median (25th–75th)*	40 (34–50)	38 (30–50)	1.33 (0.63–2.77)	0.45
Other risk factors, *n. (%)*	17 (26.2)	23 (34.8)	0.65 (0.31–1.37)	0.26
Smoking and other risk factors, *n. (%)*	17 (26.2)	20 (30.3)	0.73 (0.34–1.57)	0.42
Chronic cough and/or phlegm without dyspnoea, *n. (%)*	22 (33.8)	31 (46.9)	0.56 (0.28–1.14)	0.11
Dyspnoea, *n. (%)*	41 (63.1)	32 (48.5)	1.74 (0.87–3.48)	0.11
Previous exacerbations, *n. (%)*				0.50
Never	29 (46.8)	32 (52.5)		
Few	14 (22.6)	16 (26.2)	0.97 (0.40–2.32) 1.61 (0.68–3.83)	
Frequent	19 (30.6)	13 (21.3)		
Exacerbations per year during follow-up, *median (25th–75th)*	0.44 (0.00–0.73)	0.23 (0.00–0.59)	1.58 (0.79–3.16)	0.19
Exacerbations per year requiring hospitalization during follow-up, *median (25th–75th)*	0.10 (0.00–1.00)	0.00 (0.00–0.00)	2.57 (1.21–5.48)	**0.014**
Presence of emphysema, *n. (%)*	29 (44.6)	5 (7.5)	11.88 (3.78–37.36)	**<0.0001**
Cardiovascular co-morbidities, *n.* (%)	18 (27)	15 (23)	1.28 (0.58–2.81)	0.55
FEV_1, *L, median (25th–75th)*	1.88 (1.49–2.17)	1.63 (1.27–1.96)		**0.017**
FEV_1, *% pred., median (25th–75th)*	72 (59–78)	65 (56–72)		**0.014**
FRC, *L, median (25th–75th)*	4.21 (3.67–4.96)	3.80 (3.21–4.33)		**0.004**
FRC, *% pred., median (25th–75th)*	125 (109–140)	117 (99–127)		**0.028**
RV, *L, median (25th–75th)*	3.37 (2.92–4.05)	3.05 (2.76–3.68)		**0.030**
RV, *% pred., median (25th–75th)*	128 (113–147)	121 (109–136)		0.15
FEV_1 reversibility, *n. (%)*	19 (36)	16 (30)	1.29 (0.57–2.91)	0.54
FVC reversibility, *n. (%)*	10 (15)	7 (11)	1.51 (0.54–4.23)	0.44
Triple therapy, *n. (%)*	50 (76.9)	43 (65.2)	0.58 (0.28–1.28)	0.18
Good adherence, *n. (%)*	62 (95.4)	59 (89.4)	1.84 (0.51–6.61)	0.34

Rapid decliners were those patients with decline in FEV_1 greater than the median of the distribution of individual values. OR = Odds ratios; CI = confidence intervals; FEV_1 = forced expiratory volume in 1 second; FRC = functional residual capacity; FVC = forced vital capacity; RV = residual volume. Statistically significant *P* values are indicated in boldface type.

Table 3. Independent predictors of decline in FEV_1 (multivariable log linear model)

	Odds ratios (95% CI)	*p*-Value
Model 1		**<0.0001**
Smoking pack-years	1.02 (1.00, 1.03)	0.047
Presence of emphysema	17.76 (4.21, 74.93)	<0.001
FEV_1	3.64 (1.07, 12.38)	0.038
Exacerbations per year requiring hospitalization during follow-up	4.60 (1.53, 13.86)	0.001
Model 2		**0.002**
Smoking pack-years	1.01 (1.00, 1.02)	0.15
Residual volume	1.84 (1.04, 3.24)	0.037
FEV_1	2.93 (1.16, 7.43)	0.023
Exacerbations per year requiring hospitalization during follow-up	2.58 (0.99, 6.72)	0.052

Statistically significant P values are indicated in boldface type.

Discussion

In this study of a well-defined cohort of patients with moderate COPD under maximum medical therapy, we documented that one group had a rapid FEV_1 decline and could be identified by the presence of radiological emphysema or gas trapping, and by the amount of cigarettes smoked. The other group of patients showed an increase in their mean FEV_1 during the follow-up, thus a blunted disease progression.

From the pivotal study of Burrows and colleagues other studies have suggested that part of the phenotypic heterogeneity in COPD is due to a divergent distribution of bronchial airway (chronic bronchitis) and parenchymal disease (6,14,15). However, the tendency to lump a variety of conditions under the acronym COPD has blurred important distinctions that could be useful in clinical practice to improve our understanding of the natural history of the disease and to focus treatment strategies for different COPD phenotypes.

Many recent studies have used cluster analysis to characterize different types of airway disorders, so that they are grouped based on their differences (or similarities) without *a priori* definition (5–8). Pistolesi et al., applying a cluster analysis classification model, were able to identify, along with a continuous spectrum of clinical presentations, two distinct phenotypes of patients without fully reversible chronic airflow obstruction: one with predominant airway disease and the other with predominant parenchymal destructive changes (6).

Recently, Han et al. stated that patient outcomes, such as rapid physiologic progression as indicated by change in FEV_1, are a key component of the operational definition of the phenotype (16). Including only moderate COPD patients is the advantage in the present study as previous studies included many stages of the disease (17,18). This population was targeted because it is already well known that FEV_1 in patients with moderate COPD may decrease faster than those with severe and very severe COPD, and medications such as tiotropium can ameliorate the FEV_1 decline especially in moderate COPD (19,20). In our patients with moderate COPD under maximum inhaled therapy, the rate of decline in mean post-bronchodilator FEV_1 was about 40 mL/year, similar to that found in the large cohort of patients with moderate COPD participating in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) clinical trial (19). However, since the publication of the seminal review of Fletcher and Peto, it is well known that some subjects with COPD experience a more rapid decline in lung function than others (21). As in the large UPLIFT sample, in our patient sample a large variation in lung function decline was observed (19). This allowed us to differentiate patients under maximum inhaled therapy into two groups, "rapid decliners" and "slow decliners." Actually, a substantial minority of slow decliners had essentially no loss of lung function over at least 3 years; this remarkable finding has already been showed by Nishimura in Japanese patients and makes the universal "progressive" descriptor an oversimplification (18).

Another important result of our study is that the presence of emphysema as assessed by CT imaging is an independent predictor of rapid decline in FEV_1. To the best of our knowledge, until recently only a few studies have examined the relationship between HRCT emphysema and change in lung function with inconclusive results, mainly due to variations in sample composition, procedures for imaging acquisition and interpretation, and to different aims of the studies (18,22–24).

Our results are in keeping with Vestbo, analysing the changes in FEV_1 over a 3-year period in the notably large number of subjects participating to the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study, who recently found that patients with emphysema (as defined on the basis of CT scanning) had an excess loss of FEV_1 as compared with the study participants who did not have these conditions (17). Moreover, the important prognostic value of emphysema as assessed by HRCT imaging has been underlined also by Haruna et al. using this as an outcome of respiratory mortality (25). Another important result of our multivariable analysis is that the residual volume, the physiologic hallmark of emphysema, is significantly associated with a rapid decline. In clinical practice, this confirms the need for lung volume determination at the initial COPD assessment.

All our patients were receiving triple or double inhaled therapy in an attempt to obtain the maximum pharmacological effect on airflow obstruction and exacerbations (26). This is not recommended in the patients with GOLD stage II COPD by current guidelines, but when the study started, it was believed that such a therapy might bring a real advantage for patients with COPD and there was concern about discontinuation of inhaled corticosteroids (27,28).

At any rate, it should be noticed that also in the ECLIPSE observational study, in which all the patients were managed by their usual physicians, 72% of the patients received inhaled glucocorticoids (17). Vestbo and co-authors chose not to include treatment in their analyses, since the effects of treatment on the rate of decline in FEV_1 are likely to be confounded as a result of bias by indication and other (17). In our study, we observed impressive results in terms of reduction in lung function decline or even an improvement in the mean FEV_1 in the group of patients with predominant airway disease. Even in the absence of a control group, our results allow us to speculate that the lack of a specific selection of patients in recent large clinical trials has contributed to an underestimation of the COPD treatment effect.

In agreement with Nishimura et al., we found a very low incidence of exacerbation during the study period in all subjects groups (18). This was probably due to the moderate COPD stage and the ongoing maximal therapy. However, exacerbations requiring hospitalization during the follow-up had an effect on the rate of decline in FEV_1.

A potential limitation of our study is the relatively small sample size. However, our patients were selected with attention avoiding misclassification and overlap with other respiratory diseases, in particular, asthma. Patients were well characterized at baseline and special attention was paid to the evaluation of their attitude to collaborate and submit to lung function tests, complete the longitudinal study and adhere to therapy.

A limitation was the only use of a visual scoring system of emphysema at HRCT scan. Quantitative computerized assessment of emphysema would have provided a more consistent assessment of disease extent (29,30). However, densitometry requires dedicated software and spirometrically gated technique in order to avoid the influence of lung inflation during scanning while visual analysis is relatively independent from the technical features of the scanning protocol. Visual analysis is more operator-dependent than densitometry but consistency and accuracy of our assessment of emphysema was insured by a consensus reading (31).

For the purpose of our study we considered emphysema present when the emphysema involvement at visual scoring system was greater than 25% of lung parenchyma. This was due to the relatively small number of subject with significant emphysema that precluded a more detailed analysis and the consequent assessment of a relationship between emphysema severity and change in FEV_1. However, a positive consequence of this limitation was the reduction of the subjectivity of interpretation; this approach may more realistically represent what performed in clinical settings.

Another potential limitation was the lack of diffusing capacity of the lung for carbon monoxide. As abundantly documented in the literature, the more extensive the emphysema, and the lower the diffusion capacity. This feature is deemed to reflect the pathologic consequences of lung hyperinflation and alveolar disruption on the vascular side. We already documented that a fairly large proportion of the emphysema assessed by HRCT scan can be explained by a multiple regression model, including non-invasive lung function measurements reflecting lung hyperinflation, bronchial collapsibility, alveolar-to-capillary diffusion capacity, and bronchodilator response (30). In the present study, we choose to use only measurements of lung hyperinflation (i.e., an increase in FRC), gas trapping (i.e., an increase in RV) that are well-known as major characteristics of emphysema patients and are regarded as reflecting the quintessential feature of this disease (i.e., the decrease in lung elastic recoil).

Conclusions

The rapid FEV_1 decline may be identified by the presence of emphysema, as assessed by HRCT scans or lung function testing, in patients with a long smoking history. This supports the importance of lung volume determination at the first assessment of COPD patients and, when needed, further imaging studies. Patients with prevalent airway disease under therapy have a blunted disease progression. This improved phenotypic characterisation may prove useful both in daily practice and clinical trials, leading to different and specific pharmacological treatments and other interventions.

Declaration of interests

MP receives payment from Nycomed for board membership; he also received a personal income for lectures from companies that develop and manufacture medications for COPD (Nycomed, Boehringer, Novartis, Merk, Menarini, GSK, Chiesi) and travel funding from Boehringer and GSK. The other authors report to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. No funds declared. The authors are responsible for the content and the writing of this paper.

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