Symptomatic smokers without COPD have physiological changes heralding the development of COPD

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In symptomatic smokers with normal FEV_1/FVC, an abnormal $FEF_{25-75\%}$ (MMEF), which reflects early lung abnormalities, could be used as a biomarker for disease progression and impending risk of COPD development https://bit.ly/39y0smC

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Abstract

Background COPD is a major health problem, mainly due to cigarette smoking. Most studies in COPD are dedicated to fully developed COPD in older subjects, even though development of COPD may start soon after smoking initiation. Therefore, there is a need to diagnose this "early disease" by detecting the initial events responsible for ultimate development of COPD.

Methods Measurement of maximum mid expiratory flow between 25 and 75% of vital capacity (MMEF) in a routine spirometry, which detects small airways disease, was used to investigate if MMEF abnormalities in smokers without COPD (noCOPD) would relate to respiratory symptoms and identify smokers that might progress to COPD. For this purpose we studied 511 smokers, 302 COPD and 209 noCOPD, followed long term with spirometry including MMEF, diffusing capacity of the lung for carbon monoxide (D_{LCO}), 6-min walk test (6MWT), Medical Research Council Dyspnoea Scale and COPD Assessment Test. Three spirometries V1,V2 and V3 (5±2.5 and 10±4 years apart from V1) were performed to assess functional decline and development of COPD.

Results 65% of noCOPD had an abnormal MMEF (<80%) and 38% an abnormal D_{LCO}. The NoCOPD with MMEF <80% group performed worse in the 6MWT (p=0.01), was more dyspnoeic (p=0.01) and had higher prevalence of chronic bronchitis than the noCOPD with MMEF>80% group (p=0.04). 21% of noCOPD with MMEF <80% and 2.7% with MMEF>80% developed COPD by V3 (p=0.0004).

Conclusions The MMEF, a functional test available in a routine spirometry, can detect early lung abnormalities and identify the subset of symptomatic smokers with pathological changes that might lead to COPD.

Introduction

COPD is a major global public health problem, cigarette smoking being by far the chief etiological factor for its development. COPD can affect between 15 and 30% of smokers [1], and among those affected there is a large variation in the severity of the disease they could develop, indicating that a predisposing individual background, likely multifactorial, is the basis for both the development of the disease and its severity.

The great majority of studies in COPD have been so far dedicated to the investigation of severe COPD in older subjects, where the disease is fully developed. However, it is well established that the development of COPD may start soon after the beginning of smoking, which has emphasised the need to diagnose and

define this "early disease", in order to investigate the factors associated with and possibly responsible for disease progression and eventual severity [2, 3].

Ideally, early COPD would be defined by detecting the initial events responsible for ultimate development of pathology [2]. It has been recently described that smokers could present with clinically significant pulmonary symptoms not reflected by spirometric airflow limitation (normal forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC)) [4], and respiratory symptoms are being entertained as a surrogated form of evidence for the definition of what it has been called "early disease" [2, 3]. A subset of symptomatic smokers probably already has pathological changes in the lung that might or might not lead to COPD, but additional research is needed to identify that subgroup unambiguously [3].

If symptoms in smokers with normal FEV_1/FVC were due to structural abnormalities, their identification by easily feasible tests would be essential for their diagnosis, validation of symptoms and the monitoring of their progression [5]. Although airways abnormalities and early emphysema have been described by computed tomography (CT) in smokers with normal spirometry [6, 7], CT does not properly visualise small airways and furthermore would not be adequate for large populations studies. However, detecting early small airways disease and assessing its progression might be accomplished using sensitive, but not readily available, tests such as single breath nitrogen washout and impedance oscillometry [8], or by simpler tests sensitive to small airways abnormalities available in a routine spirometry, like the maximum mid expiratory flow at 25–75% of FVC (MMEF) (also known as FEF25–75) and the transfer factor of the lung for carbon monoxide D_{LCO} [9, 10]. An abnormal MMEF is an early feature of lung disease in patients with α-1 antitrypsin deficiency associated with faster decline of FEV_1 [11], and recently MMEF has been shown to be associated with emphysematous changes and airway abnormalities in a cohort of smokers with and without COPD [12]. However, the value of MMEF in the detection of lung abnormalities and their possible progression in smokers without COPD (FEV_1/FVC >70%) has never been investigated.

Based on those premises we hypothesise that: 1) MMEF abnormalities in smokers without COPD would relate to the respiratory symptoms; and 2) MMEF abnormalities might identify smokers that would eventually progress to COPD.

For this purpose, we used an ongoing cohort of smokers with and without COPD, free of significant comorbid conditions at recruitment, in which consecutive functional measurements over 10 years of follow-up were available.

Methods

Study population

Participants were recruited among smokers who first attended the Pulmonary Clinic at the Hospital Universitario Miguel Servet (Zaragoza, Spain) requesting to be included in a smoking cessation programme or referred by other doctors to assess their respiratory health between October 2010 and April 2014. The inclusion criteria are detailed in supplementary figure E1.

At baseline, all subjects were clinically stable, free of major comorbidities, not having had any exacerbations for at least 8 weeks (details in supplementary material). Subjects with asthma or history of asthma, bronchiectasis, autoimmune diseases, haematological diseases, other respiratory diseases or coexisting malignancy at recruitment were excluded. All subjects underwent a comprehensive clinical and functional examination including spirometry, maximum mid-expiratory flow at 25–75% of FVC (MMEF), measurement of diffusing capacity of the lung for carbon monoxide (D_{LCO}), using the Communauté Européenne du Charbon et de l'Acier (CECA) as predicted values [13]. The 6-min walk test (6MWT), modified Medical Research Council (mMRC) Dyspnoea Scale and COPD Assessment Test (CAT) [14] were also obtained.

COPD was defined by FEV_1/FVC <70% [1] and smokers without COPD (noCOPD) by FEV_1/FVC >70% post-bronchodilator. In noCOPD subjects, the baseline visit spirometry (V1) was compared to a second (V2) and a third (V3) spirometry performed after 5±2.5 (V2) and 10±4 (V3) years of follow-up to assess functional decline over time and the potential development of COPD. Patients with COPD at baseline had a second spirometry after 10±4 years of follow-up to assess functional decline.

Chronic bronchitis was defined as the presence of cough and sputum production for at least 3 months in each of two consecutive years [1]. Annual frequency and type of exacerbations were collected. The study

was approved by human research review board (IRB.12/2010), and all patients provided informed written consent before any procedure was done.

Statistical analysis

Patient's characteristics were described using mean±SD or median (interquartile range) for continuous variables and counts and percentages for categorical variables. For continuous variables, normal distributions were tested using the Shapiro–Wilk test. Comparisons among groups were evaluated with Mann–Whitney U-tests or Kruskal–Wallis test as appropriate. Distributions of categorical variables were compared with the χ^2 test. The lower limit of normal (LLN), which represents the 5th percentile and is defined as −1.645 z-score value, was calculated for FEV_1/FVC [15–17]. Correlation coefficients were calculated using the nonparametric Spearman's rank method. In noCOPD patients we performed the repeated measurements ANOVA to evaluate the difference in FEV_1 decline in the follow-up period.

A multivariate logistic regression was performed in smokers without COPD to detect possible significant predictors of COPD development and FEV_1 decline at follow-up.

All analyses were performed using SPSS (version 25.0.0.1 for Windows). Statistical significance was assumed for a p-value <0.05.

Results

Among the 511 smokers included in the study, 302 (59%) had COPD (COPD) and 209 (41%) did not (noCOPD), since FEV_1/FVC was >70%, a value very similar to the 71% obtained by calculating the LLN using the z-score [16–18]. Smokers with COPD were older, smoked more and had a higher prevalence of chronic bronchitis than noCOPD (45% *versus* 27%; p=0.001). The prevalence of chronic bronchitis was similar in all COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages. As expected, FEV_1, MMEF and D_{LCO} values were lower in COPD than in noCOPD (table 1). The therapy received by the subjects in both groups is shown in supplementary table E1. A higher proportion of COPD than noCOPD received treatment, and triple therapy was used significantly more in noCOPD with MMEF <80% than in those with MMEF >80%.

TABLE 1 Clinical and functional characteristics of all smokers, smokers without COPD (noCOPD) and with COPD (COPD)

	All smokers	NoCOPD	COPD	p-value
Subjects n	511	209	302	
Male	423 (83)	147 (70)	276 (91)	0.001
Age years	58±10	52±11	62±8	0.001
Smoking history pack-years	43±24	35±19	49±25	0.001
FEV_1 post-bronchodilator L	2.34±0.85	2.88±0.78	1.96±0.67	0.001
FEV_1 post-bronchodilator (% pred)	79±22	95±5	68±19	0.001
FEV_1/FVC post-bronchodilator %	64±15	78±5	54±11	0.001
MMEF 25–75 post-bronchodilator % pred	47±29	75±21	27± 3	0.001
D_{LCO} % pred	80±21	86±17	76±22	0.0001
Decline of FEV_1 per year mL year^{-1}	32±46	33±37	31±52	NS
Subjects with chronic bronchitis	193 (38)	56 (27)	137 (45)	0.001
Subjects with mMRC ⩾2	214 (42)	71 (34)	143 (47)	0.006
mMRC score	1.33±0.70	1.10±1.19	1.50±1.09	0.0001
CAT score	9.7±7.3	9.0±6.9	10.2±7.1	0.042
Distance at 6 min walk test m	419±122	481±114	376±109	0.001
Number of total exacerbations per year	0.79±1.54	0.49±1.05	1.00±1.78	0.001
Number of severe exacerbations per year	0.05±0.14	0.03±0.09	0.06±0.17	0.024
Subjects who developed comorbidities	418 (82)	160 (77)	258 (85)	0.001
GOLD 1			81 (27)	
GOLD 2			169 (56)	
GOLD 3–4			52 (17)	

Data are presented as number (%) or mean±SD. p-value refers to Mann–Whitney test or χ^2 test, for comparisons between noCOPD and COPD. NS: nonsignificant; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MMEF: maximum mid-expiratory flow at 25–75% of FVC; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

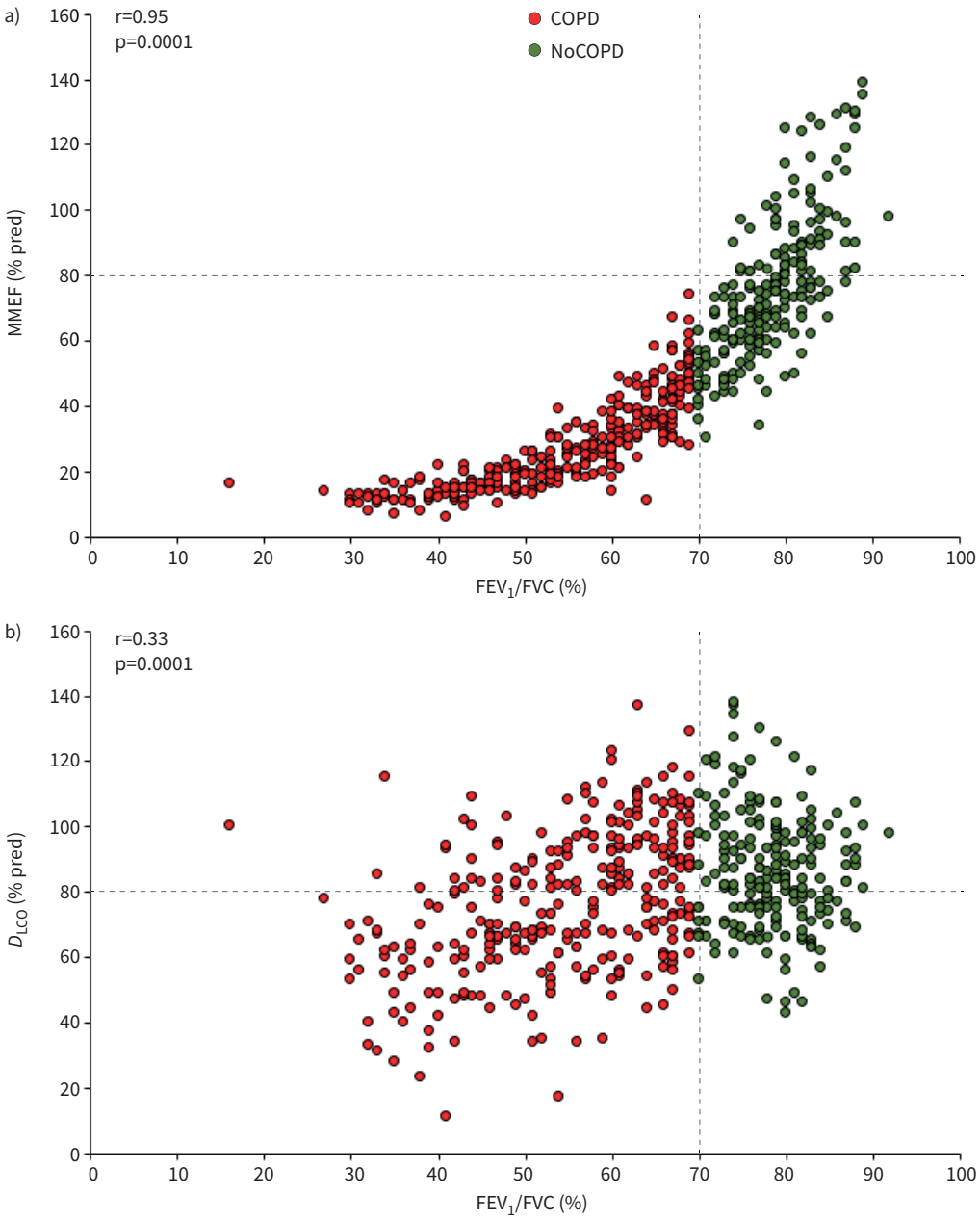

FIGURE 1 a) Relation between FEV_1/FVC (%) and MMEF in the whole population at the first spirometry (V1). Normal values for FEV_1/FVC (>70%) and MMEF (>80%) are outlined. 65% of the subjects with noCOPD (FEV_1/FVC >70%) had an abnormal MMEF (<80% predicted). b) Relation between FEV_1/FVC (%) and D_{LCO} (%) in the whole population at the first spirometry (V1). Normal values for FEV_1/FVC (>70%) and D_{LCO} (>80%) are outlined. 38% of subjects without COPD had an abnormal D_{LCO}. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MMEF: maximum mid-expiratory flow; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

Functional changes in smokers without COPD

The relation between FEV_1/FVC and MMEF in the whole population at the first spirometry (figure 1a) showed that 65% of the subjects with noCOPD had an abnormal MMEF (<80% predicted) [11, 12, 19], indicating airflow obstruction secondary to abnormalities of small airways or decrease in elastic recoil or both. When the noCOPD group was divided according to MMEF >80% (normal) or <80% (abnormal), those with MMEF <80% were older, had a higher body mass index and had smoked more. The proportion of active smokers was similar in the two groups (table 2).

The D_{LCO} was abnormal (<80% predicted) in 38% of smokers with noCOPD (figure 1b), further defining a significant and detectable lung abnormality in smokers without COPD. NoCOPD subjects with abnormal D_{LCO} had a lower MMEF, a higher proportion of CAT score >10 (44% *versus* 27%; p=0.01) and a higher MRC dyspnoea score (1.34±1.17 *versus* 0.95±1.18; p=0.007) than noCOPD with normal D_{LCO} (supplementary table E2).

Relation of functional abnormalities to symptoms

Clinically, noCOPD with MMEF <80% performed significantly worse in 6MWT (459±109 *versus* 519 ±114 m; p=0.01), were more dyspnoeic (1.23±1.19 *versus* 0.85±1.15 dyspnoea score; p=0.01, figure 2a), had a higher number of total exacerbations per year (0.56±1.12 *versus* 0.36±0.91; p=0.04) and a higher prevalence of chronic bronchitis than noCOPD with MMEF >80% (31% *versus* 19%; table 2). The CAT score was similar in noCOPD smokers regardless of the MMEF (< or >80%), and its value was influenced by the presence of chronic bronchitis: in the MMEF <80% population, those with chronic bronchitis had a higher CAT score than those without chronic bronchitis (13.95±6.63 *versus* 7.37±5.76; p=0.0001; supplementary figure E2).

Subjects with noCOPD and MMEF <80% with chronic bronchitis had similar smoking history than those without chronic bronchitis, but more of them were active smokers (62% *versus* 39%; p=0.01). The proportion of subjects with MRC dyspnoea score >2 (55% *versus* 28%; p=0.003), and the raw MRC dyspnoea score (1.69±1.19 *versus* 1.02±1.14; p=0.002; figure 2a and b) were higher and the D_{LCO} lower (78.45±16.5 *versus* 87.10±18.27; p=0.007) in the MMEF <80% group with chronic bronchitis than in those without. The total number of exacerbations per year was also higher in the MMEF <80% group with chronic bronchitis (0.87±1.44 *versus* 0.41±0.9; p=0.002).

FEV_1 decline and COPD development

21% of noCOPD with MMEF <80%, half of them younger than 50 years, developed COPD by the time of the third visit (V3), with a fall of FEV_1/FVC from 73.1±2.8% to 62.6±5.7% and a FEV_1 decline of 52 ±23 mL·year^{-1}, while only 2.7% of the noCOPD with MMEF >80% developed COPD at V3 (p=0.001). Of interest, 85% of the noCOPD with MMEF <80% who developed COPD at V3 had already developed COPD by the second visit (V2). The FEV_1 decline in noCOPD with MMEF <80% who did not develop COPD was 24±34 mL·year^{-1}, while in those who did develop COPD the decline was 52±23 mL·year^{-1}

TABLE 2 Subjects without COPD (noCOPD) according to maximum mid-expiratory flow (MMEF) above and below 80%

	NoCOPD MMEF <80%	NoCOPD MMEF >80%	p-value
Subjects n	135	74	
Age years	54.05±11.05	47.82±9.31	0.01
BMI kg·m^{-2}	28.75±4.99	27.18±4.95	0.01
Smoking history pack-years	45.17±25.57	38.10±20.92	0.048
Active smokers, n (%)	61 (45)	33 (45)	NS
CAT score	9.42±6.84	8.24±6.94	NS
Subjects with CAT ⩾10, n (%)	47 (35)	23 (31)	NS
Distance at 6MWT m	459±109	519±114	0.01
Number of total exacerbations per year	0.56±1.12	0.36±0.91	0.04
Subjects with CB n (%)	42 (31)	14 (19)	0.04
Subjects with mMRC ⩾2, n (%)	49 (36)	22 (30)	NS
mMRC score	1.23±1.19	0.85±1.15	0.01
Subjects with D_{LCO} <80%	56 (41)	24 (32)	NS
D_{LCO} % pred	84± 18	89±17	NS
FEV_1 % pred	90.74±12.74	105.11±12.74	0.0001
FEV_1/FVC %	76.39±3.9	82.31±3.89	0.0001
Subjects who develop COPD at V3, n (%)	28(21)	2(2.7)	0.001

Data are presented as n (%), and mean±SD. p-value refers to Mann–Whitney test or χ^2 test. NS: nonsignificant; BMI: body mass index; CAT: COPD Assessment Test; 6MWT: 6-min walk test; CB: chronic bronchitis; mMRC: modified Medical Research Council; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; V3: third visit..

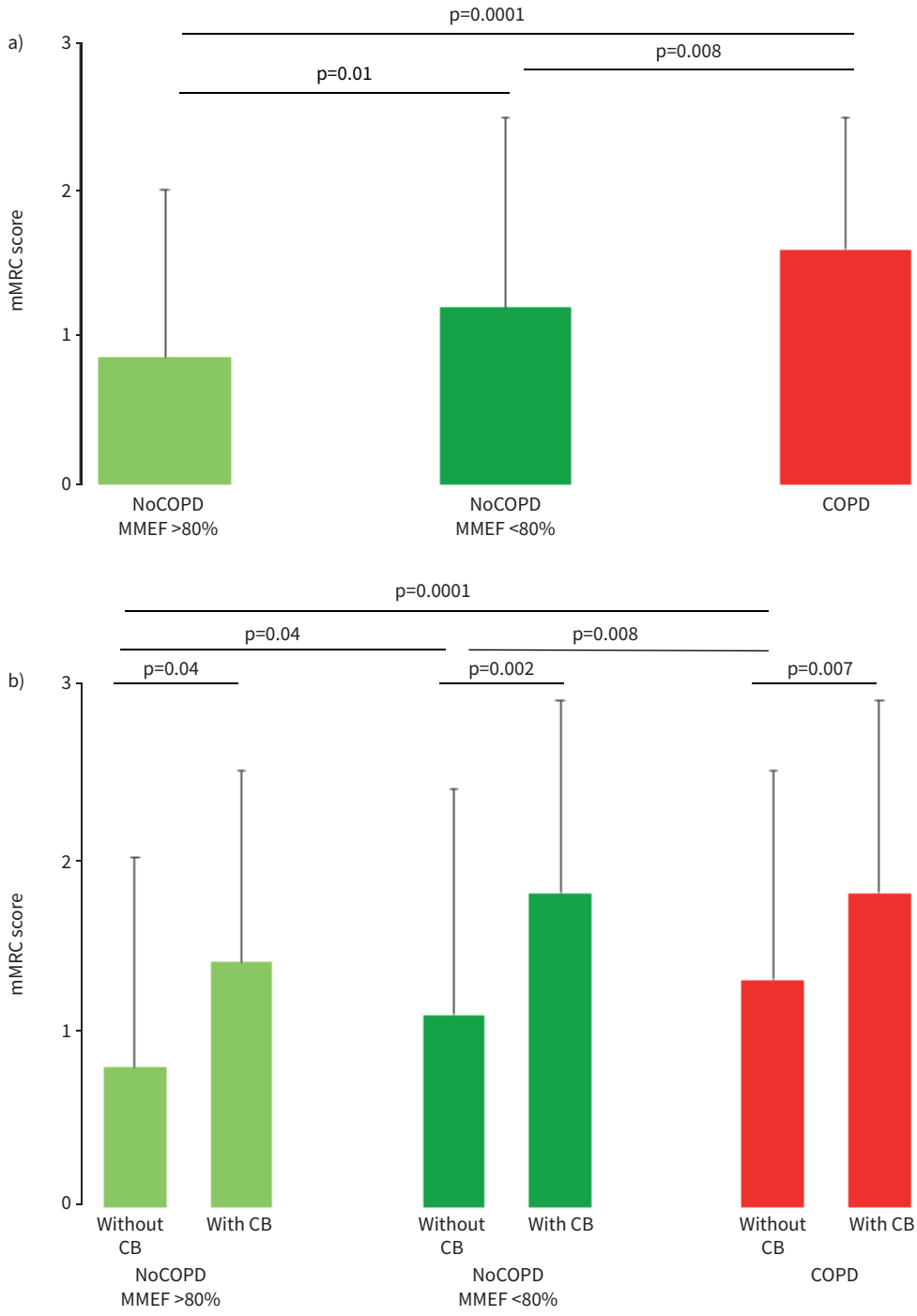

FIGURE 2 a) Mean MRC dyspnoea score in subjects without COPD with MMEF >80%, MMEF <80% and COPD (Kruskal–Wallis test p=0.0001). b) The presence of chronic bronchitis (CB) in all groups significantly worsens the severity of the baseline dyspnoea score (Kruskal–Wallis test p=0.0001). The effect of CB in the deterioration of the dyspnoea is better understood by considering CB not only as sputum production but also as part of the diffuse "muco-obstructive" disease that affects all airways [22, 23]. Histograms represent mean±SD. MMEF: maximum mid-expiratory flow at 25–75% of FVC; mMRC: modified Medical Research Council.

(p=0.0001; table 3). The proportion of subjects with chronic bronchitis and the CAT score were not significantly different between noCOPD with MMEF <80% who developed COPD and those who did not develop it, while the MRC dyspnoea score was higher in those who developed COPD.

TABLE 3 Subjects without COPD (noCOPD) with maximum mid-expiratory flow (MMEF) <80% with and without progression to COPD

	NoCOPD MMEF <80% who did not develop COPD	NoCOPD MMEF <80% who developed COPD	p-value
Subjects n	107	28	
Age years	54.2±11.4	53.3±9.9	NS
Smoking history pack-years	35.9±19.6	36.3±14.8	NS
Active smokers, n (%)	45 (42)	15 (53)	NS
mMRC score	1.1±1.1	1.8±1.2	0.001
FEV_1 % pred	90.3±12.8	89.5±12.4	NS
FEV_1/FVC %	77.2±3.1	73.1±2.8	0.0001
Decline of FEV_1 per year ($mL \cdot year^{-1}$ from V1 to V3)	24±34	52±23	0.0001

Data are presented as n (%) or mean±SD. p-value refers to Mann–Whitney test or χ^2 test. NS: nonsignificant; mMRC: modified Medical Research Council; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Acknowledging that MMEF is a very sensitive but also highly variable test in the detection of small airway disfunction, we have also looked at the MMEF cut-off of 60% predicted, to provide a further insight into the interpretation of the data. As expected, the number of patients with MMEF <60% (26% of the 209 noCOPD) is lower but the percentage of those developing COPD by V3 is higher at 31% compared to the 21% developing COPD when the cut-off was at 80%. All these changes were seen while both the FEV_1 (85%) and the FEV_1/FVC (72%) were still within normal limits (supplementary tables E3 and E4). Furthermore, a logistic regression analysis in smokers without COPD showed that MMEF at V1 was the only factor associated with COPD development (p=0.001) and with lung function decline (p=0.03) at follow-up, results that support the importance of the MMEF as a biomarker for disease progression (supplementary table E5).

The FEV_1 decline in the COPD group was very variable, variability accounted for in part by the presence of chronic bronchitis, since COPD with chronic bronchitis declines more than COPD without chronic bronchitis (41±48 *versus* 22±53 $mL \cdot year^{-1}$, p<0.01) and in part by the smoking activity, since active smoking further accelerates FEV_1 decline. In the presence of chronic bronchitis, ex-smokers declined less than active smokers (48.5±47.9 *versus* 31.6±45.1 $mL \cdot year^{-1}$, p<0.01; supplementary figure E3).

Discussion

In our population of smokers without COPD, 65% had an abnormal MMEF indicating airflow obstruction at the level of the small airways, and 38% had an abnormal D_{LCO}, a manifestation of V′/Q′ mismatching. The evident pathological abnormalities present in the lung before the spirometric diagnosis of COPD were correlated with the clinical and symptomatic profile in smokers without COPD. Furthermore, 21% of smokers without COPD with an abnormal MMEF (half of them younger than 50 years) developed COPD during the follow-up, an important finding that alerts to a possible progression to COPD in these smokers.

Recent literature has underlined that smokers without COPD, or preserved pulmonary function, can present with significant respiratory symptoms [4, 20], which it has been suggested could be defined as the initial events heralding the ultimate development of pathology before spirometry becomes abnormal [3, 7]. Yet a more comprehensive use of all the spirometric data could be helpful in this regard.

It is well accepted that the earliest lung abnormalities produced by cigarette smoking affect bronchioles <2 mm in diameter – the small airways – which contribute <30% to the flow resistance in normal lungs [9]. Thus, small airways abnormalities could be present in smokers well before the FEV_1/FVC% becomes abnormal [21, 22], and could be detected by parameters available in a routine spirometry like the MMEF [9, 22].

The significance of the pathological abnormalities reflected by the abnormal MMEF and D_{LCO} is underlined by the lower distance walked in the 6MWT, the higher dyspnoea score and the higher number of exacerbations in smokers without COPD.

How does small airways dysfunction fit into this scenario? The first evidence of the pathophysiological role of the small airways abnormalities was demonstrated by studies on the frequency-dependence of dynamic compliance by Woolcock and Macklem [23]. Essentially the heterogeneous distribution of the

small airways abnormalities throughout the lung, with some airways remaining more obstructed than others during the ventilatory phase, would result in some regions of the lung moving during the respiratory cycle out of phase with others. As a result, slow regions will have smaller tidal volumes than the fast ones, which would result in significant abnormalities in ventilation distribution and gas exchange, especially as frequency of breathing increases [24].This would mean that, as requirement for ventilation increases, the volume of lung participating in ventilation decreases, with the consequent dynamic hyperinflation, which becomes the physiological basis for dyspnoea and decreasing exercise ability [25].

The abnormalities in D_{LCO} at this stage of disease are not surprising, since the D_{LCO} is influenced not only by the surface area for gas exchange, but also by ventilation distribution and ventilation/perfusion (mis) matching. Impaired perfusion in emphysema-free areas [26], by vascular compression in patchy areas of localised gas trapping due to small airway dysfunction, may decrease D_{LCO} [27]. A low D_{LCO} signals high ventilation/perfusion (increased dead space) which underpins the excessive ventilation and dyspnoea described in subjects with low D_{LCO} [28, 29]. Abnormalities in D_{LCO} in smokers with normal spirometry and the increased risk of these patients to develop COPD have been described before [10].

The MMEF measures the flow between 25 and 75% of FVC, in which flow is determined by the resistance of the small airways and the elastic recoil pressure of the lung. Thus abnormalities in the MMEF, a test that has been shown to reflect these "initial" lung pathological abnormalities, could explain the symptomatic manifestations found in smokers with noCOPD [9, 21, 30, 31]. Small airways abnormalities in symptomatic smokers without COPD have been described by CT scans [3, 6, 9], and were significantly associated with low MMEF in another study [12]. Furthermore, in α-1 antitrypsin-deficient subjects, a reduction of MMEF, likely due in part to losses of elastic recoil and in part to small airways abnormalities [11, 32, 33], was associated with impaired health status and greater risk of disease progression [32]. These results show how the MMEF might provide important insights into the underlying lung pathology before COPD is evident.

The important contribution of chronic bronchitis to the clinical presentation of smokers with noCOPD could be better understood by considering chronic bronchitis as part of the so-called "muco-obstructive" disease [34], a disease characterised by abnormally raised mainly MUC5AC mucin concentrations [35], increased sputum production and mucus hyperconcentration that are central to the pathogenesis of chronic bronchitis [34–36]. Accumulated mucus could form mucus plaques and plugs within airway lumens serving as the nidus for inflammation, intermittent infection and airflow obstruction [35–37]. Luminal plugging has been identified by CT scan as a frequent finding significantly associated with chronic bronchitis, a finding that may play an important role in the pathophysiology of airflow obstruction in smokers, even without COPD [38].

The abnormal MMEF in smokers without COPD illustrates that smokers could and would develop small airways abnormalities not detected by the FEV_1, and importantly that a significant percentage of noCOPD smokers with abnormal MMEF, half of them younger than 50 years, would develop COPD over time. We found a large variation in MMEF in the noCOPD subjects with normal FEV_1/FVC and FEV_1, a variability that has been defined as "noise" and has hence detracted from the use of the MMEF as a diagnostic tool for early lung abnormalities in smokers. However, in our study we showed that the noCOPD with MMEF <80% group were more symptomatic and had lower FEV_1/FVC, even if still within normal limits, than those with MMEF>80%. Furthermore, 21% of noCOPD with abnormal MMEF did develop COPD at follow-up, while only 2.7% of those with normal MMEF did. These results were confirmed using a MMEF <60% cut-off (at which 31% of subjects developed COPD at follow-up) and with a logistic regression analysis that identified MMEF at baseline as the only factor associated with COPD development. These findings suggest that the variability of MMEF has an anatomical basis and hence ought to be considered "signal" rather than "noise".

Since early small airways abnormalities detected by a lower MMEF do progress in a significant proportion of smokers to overt COPD, we believe that these patients ought to be carefully monitored. In our population of noCOPD smokers, we could identify three groups using the MMEF: a group with MMEF >80% (no disease), a group with MMEF<80% (abnormal lung pathology) but no progression to COPD and a group with MMEF <80% (abnormal lung pathology) with progression to COPD, which very likely represent three different susceptibility factors for the development of disease that could be investigated.

In our cohort of patients with COPD, having chronic bronchitis and being active smokers, as previously shown [6, 39–41], had important consequences in the disease progression. FEV_1 decline in COPD patients with chronic bronchitis was about twice the decline in those without chronic bronchitis, and this was

further accentuated when, besides having chronic bronchitis, these patients were also active smokers (supplementary figure E3a-c). These data, by showing the important effects of actively smoking in the progression of the disease, underline the importance of the smoking cessation measures in these patients, as outlined in the European Respiratory Society document [42]. Contrary to the findings in smokers with COPD, neither chronic bronchitis nor active smoking could predict a faster fall in FEV_1 over time and the eventual development of COPD in smokers without COPD (supplementary table E5), underlining the importance of other factors governing susceptibility for the development of the disease in these subjects [43].

Being a single centre study and a relatively small cohort are possible limitations of our study. Nonetheless, having a population of smokers with a mean age of 53 years carefully followed longitudinally by the same group of physicians for 10 years ensures an evenness in the data collection with protocols available to clinical practices. The lack of a replication cohort may detract from the value of the study; however, since the original hypothesis was novel, we thought it would be first necessary to "test" our point before a replication cohort could be done. Acknowledging that MMEF is a very sensitive but also highly variable test in the detection of small airway dysfunction, besides the MMEF <80% we also looked at the MMEF cut-off of 60% predicted, to provide a further insight into the interpretation of the data, which solidified the main results of the study. MMEF <80% predicted was used to define abnormality in order to allow comparisons with other studies [11, 12, 19] and because it would be more practical, since it is the way it is reported in most laboratories.

In conclusion, our study shows that the analysis of MMEF, a simple and ancillary lung function test today considered obsolete, is an easy and important step to detect existing lung abnormalities and could be used as a biomarker to identify the subset of symptomatic individuals with pathological changes that might lead to COPD. Furthermore, since the abnormality of this test reflects potentially reversible inflammatory changes in the small airways, it could be used for the follow-up of possible treatment response.

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