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Cardiopulmonary exercise testing and second-line pulmonary function tests to detect obstructive pattern in symptomatic smokers with borderline spirometry

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ABSTRACT

Background: The need for additional research on symptomatic smokers with normal spirometry has been recently emphasized. Albeit not meeting criteria for Chronic obstructive pulmonary disease (COPD) diagnosis, symptomatic smokers may experience activity limitation, evidence of airway disease, and exacerbations. We, therefore, evaluated whether symptomatic smokers with borderline spirometry (post-bronchodilator FEV_1/FVC ratio between 5th to 20th percentile of predicted values) have pulmonary function abnormalities at rest and ventilatory constraints during exercise.

Methods: 48 subjects (aged 60 ± 8 years, mean ± SD, 73% males, 16 healthy, and 17 symptomatic smokers) underwent cardiopulmonary exercise testing (CPET), body plethysmography, nitrogen single-breath washout test (N_2SBW), lung diffusion for carbon monoxide (DLCO), and forced oscillation technique (FOT).

Results: Compared to healthy subjects, symptomatic smokers showed: 1) reduced breathing reserve (36 ± 17 *vs.* 49 ± 12%, P = 0.050); 2) exercise induced dynamic hyperinflation (−0.20 ± 0.17 *vs.* −0.03 ± 0.21 L, P = 0.043); 3) higher residual volume (158 ± 22 *vs.* 112 ± 22%, P < 0.001); 4) phase 3 slope at N_2SBW (4.7 ± 2.1 *vs.* 1.4 ± 0.6%, P < 0.001); 5) no significant differences in DLCO and FOT results.

Conclusions: In smokers with borderline spirometry, CPET and second-line pulmonary function tests may detect obstructive pattern. These subjects should be referred for second line testing, to obtain a diagnosis, or at least to clarify the mechanisms underlying symptoms. Whether the natural history of these patients is similar to COPD, and they deserve a similar therapeutic approach is worth investigating.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. According to WHO estimates, 65 million people have moderate to severe COPD, with a marked heterogeneity in prevalence rates due to differences in survey methods and diagnostic criteria [1,2]. Tobacco smoking is by far the single most important risk factor for COPD [3].

The need for additional research on smokers with respiratory symptoms (dyspnoea, cough, or sputum production) and normal spirometry has recently been emphasized [4]. Despite these subjects do not meet the criteria for COPD diagnosis (i.e. a ratio of forced expiratory volume in 1 s, FEV_1, to forced vital capacity, FVC, after bronchodilator use <0.7, or below the lower limit of normal, LLN) [5], they experience exacerbations, activity limitation, and evidence of airway disease [6]. Whether these subjects have early lung function abnormalities, and a natural history similar to COPD patients, requires investigation. International documents highlight the importance of early diagnosis for optimal management of COPD

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[1,2]. Prevention strategies should be given the highest priority in order to reduce exposure to risk factors. Indeed, smoking cessation remains the most cost-effective disease-modifying intervention [7]. Notably mild patients have faster FEV_1 decline and, therefore, drug treatments are likely to be more effective in the early stages of the disease [8].

Since COPD severity mirrors the progression of the "small airways disease" (<2 mm in diameter) [9], spirometry could be less sensitive than other pulmonary functional tests, such as plethysmography, nitrogen washout, or forced oscillation technique [10]. Small airways dysfunction is associated with delayed mechanical time constants for lung ventilation, notably during exercise. Thus, similarly to COPD, pulmonary gas trapping and dynamic lung hyperinflation during exercise may represent early manifestations of peripheral airway dysfunction [11]. In symptomatic non-COPD smokers, Elbehairy et al. found greater exertional dyspnoea and lower exercise tolerance compared to healthy controls, with evidence of greater airways resistance, contractile diaphragmatic effort, and fractional inspiratory neural drive to the diaphragm [12].

Hence, the aim of our study was to investigate whether symptomatic smokers with borderline FEV_1/FVC ratio have impaired exercise capacity and lung function abnormalities similarly to COPD patients.

2. Methods

This was a case-control physiological study carried out at the Respiratory Unit of San Paolo Hospital (Milan, Italy). Local ethics committee approved the study. Written consent was obtained from each participant. No extramural funding was used to support the study.

2.1. Study population

We enrolled 3 groups of subjects: 1) consecutive outpatient smokers (active or former smokers with a smoking history ≥20 pack-years) complaining of exertional dyspnea (modified Medical Research Council, MRC, ≥2), without pre-existing conditions that could justify the symptom or provoke exercise limitation (i.e., allergy, familiar or personal history of asthma, metabolic, cardiovascular, neuromuscular, musculoskeletal, or other respiratory diseases), with spirometry values borderline for obstruction (post-bronchodilator FEV_1/FVC between the 5th and the 20th percentile of predicted values, i.e. z-score between −0.85 and −1.64); 2) consecutive mild to moderate patients with COPD diagnosis according to ATS/ERS guidelines (i.e. post-bronchodilator FEV_1/FVC < LLN) attending scheduled follow-up consultation with FEV_1>50%, age-, and sex-matched to group 1; 3) healthy subjects: asymptomatic subjects, never or former smokers with a smoking history <10 pack-years, with normal spirometry values (FEV_1/FVC, FEV_1, and FVC > LLN). Exclusion criteria for group 1 and 2 were: asthma history, relevant contraindications to clinical exercise testing, COPD exacerbations within the last 4 weeks, treatment with beta-blockers, high IgE values, or hypereosinophilia, and patients' inability to perform the study protocol. Symptomatic subjects and COPD patients were recruited among outpatients attending the Respiratory Unit of San Paolo Hospital (Milan, Italy), whilst healthy subjects were enrolled from the local community.

2.2. Study design

The first visit included questionnaires and familiarization to testing procedures. On a second day patients performed pulmonary function tests and incremental cardiopulmonary exercise. Before testing, subjects were asked to avoid the ingestion of alcohol, caffeine-containing products, and heavy meals, for at least 4 h, and to refrain from strenuous activity for at least 12 h.

2.3. Symptoms and comorbidities assessment

All subjects underwent careful medical history evaluation and symptoms assessment. Specifically, dyspnea was estimated using the Italian version of the modified Medical Research Council dyspnea scale (mMRC). The overall health status was assessed by using the COPD Assessment Test (CAT), an 8 items questionnaire. CAT score ranges from 0 to 40, with the higher scores, reflecting a greater burden of disease. Comorbidities were evaluated by Charlson comorbidity index, in which a higher score indicates greater coexisting conditions [13].

2.4. Exercise and pulmonary function tests

On the second day, subjects performed forced and slow vital capacity manoeuvers, body plethysmography and lung diffusion for carbon monoxide (DLCO) in accordance with ATS/ERS guidelines [5,14,15], and nitrogen single-breath washout test (N_2SBW), as modified by Anthonisen and colleagues (Med Graphics Elite spirometer, USA). Tidal breathing respiratory mechanics was assessed by a multi-frequency (5- 11–19 Hz) forced oscillation technique (FOT) commercially available device (Resmon Pro Restech, Milan, Italy), according to ERS recommendations [16]. Flow limitation was defined as ΔXrs (i.e. inspiratory *minus* expiratory reactance, Xrs, at 5 Hz) < 2.53 $cmH_2O/(L/s)$ [17].

Symptom-limited cardiopulmonary exercise testing (CPET) was conducted on an electromagnetically braked cycle ergometer (VMax Spectra, Sensormedics, USA) [18]. CPET consisted of a steady-state resting period and a 1-min warm-up of unloaded pedalling followed by an incremental protocol. All CPETs were concluded at the point of symptom limitation, at which subjects indicated the main reason for terminating the exercise. Breathing reserve was calculated as the difference between the maximum expiratory minute ventilation reached during CPET and the maximum voluntary ventilation. Changes in end-expiratory lung volume (EELV) were estimated from inspiratory capacity (IC) measurements performed at rest and every 2 min during the test. Dynamic hyperinflation was defined as a decrease of >150 ml in IC during exercise compared to resting levels [19].

2.5. Statistical analysis

The results are expressed as mean ± standard deviation (SD), unless otherwise stated. We calculated a sample size of 15 patients per group to detect a decrease of 15 L/min of breathing reserve compared to an expected value of 50 ± 15 L/min in healthy subjects, with a power of 80%; given an expected rate of drop out, or missing data, of 10–15% we decided to enroll 17 patients per group. Before data analysis, Lilliefors corrected K-S test was performed to examine the distribution of the residuals of the parametric tests. Quantitative variables were analyzed using analysis of variance (Anova), or Kruskal-Wallis test when appropriate. For clarity purposes, in figure and tables the label "Anova" was reported in all cases. In case of $P < 0.05$, post hoc comparisons were carried out by *t*-test with Bonferroni adjustment or Wilcoxon test. For qualitative variables, we used either a chi-square or a Fischer exact test. All tests were two-sided, and P values < 0.05 were considered statistically significant. Statistical tests were performed using the Statistical Package for Social Sciences (version 21.0; SPSS, USA).

3. Results

We enrolled 51 consecutive subjects (17 patients per group); two COPD patients and one healthy subject dropped out (one COPD patient and the healthy subject for mouthpiece intolerance during CPET, while the second COPD patient because of an acute exacerbation). Table 1 illustrates patient characteristics. The groups were matched for age and sex.

3.1. Exercise testing

Table 2 displays CPET results. Most of the exercise parameters - except anaerobic threshold and VE/VCO_2 intercept - differed significantly with Anova. In comparison with the healthy, symptomatic subjects had a lower peak oxygen consumption and a borderline significant erosion of breathing reserve ($P = 0.050$), even if the overlap of single patients results between groups was high (Fig. 1). Ten (59%) symptomatic subjects showed significant hyperinflation during exercise (Table 2). Breathing efficiency during exercise (i.e. VE/VCO_2 slope) was impaired in COPD patients, but no difference was noted between symptomatic and healthy subjects.

3.2. Second-line pulmonary function tests

With the exception of FEV_1/FVC ratio, which was an inclusion criterion, most of the measured parameters significantly differed between symptomatic and healthy subjects (Table 2). The change in FEV1 after bronchodilation (albuterol 400 mcg) was on average < 200 ml and <12% of basal values for both symptomatic subjects and COPD patients (Table 3). Compared to the healthy, symptomatic subjects exhibited higher residual volumes and reduced $FEF_{25-75\%}$ values (Table 3). It is worth of notice that the overlap of between-groups results was very low (Fig. 1). We did not find any significant difference in terms of DLCO. Nitrogen single-breath washout phase 3 slope results were significantly different between symptomatic and healthy subjects (Table 3). Fig. 1 shows that most of the symptomatic, but none of the healthy subjects had a N_2SBW slope >2.8%. As reported in Table 4, forced oscillation technique detected a mechanical impairment in COPD patients. However, the FOT results of symptomatic subjects were not significantly different from those of the healthy subjects (figure reports mean, and single patients, results of Rrs_{5-19}).

4. Discussion

The novel finding of our study is that CPET and second line pulmonary function tests detect obstructive features in symptomatic smokers with borderline spirometry. In comparison with healthy subjects, this group shows: 1) a reduction of breathing reserve and oxygen consumption, and exercise induced dynamic hyperinflation; 2) increased residual volume and N_2SBW phase 3 slope.

In real life, symptomatic smokers often use a range of respiratory medications outside of their clinical indication [6]. Recently, Elbehairy et al. studied the mechanisms of exertional dyspnea in these subjects without finding differences in ventilator requirement, operating lung volume, SpO_2 and exercise cardio-circulatory responses [12]. In contrast, we found a significant exercise induced dynamic hyperinflation. A possible explanation is in the spirometric inclusion criteria. Elbehairy A. et al. selected subjects with a normal spirometry (FEV_1 of 101 ± 13%, and FEV_1/FVC ratio of 0.73 ± 0.05, 100 ± 7%), while our subjects had a higher *a priori* risk of obstructive features, as they were selected by having a FEV_1/FVC ratio between the 5th and the 20th percentile of predicted values. Dynamic hyperinflation, even if not entirely specific [20], can also be detected in mild COPD and represents the hallmark of the

Table 1
Baseline subjects' characteristics.

	Healthy	Symptomatic	COPD	P Anova*	P Symptomatic *vs.* Healthy
Number of subjects	16	17	15	–	–
Age, yrs	59 ± 7	60 ± 10	63 ± 6	0.338	–
Male, n (%)	10 (62)	12 (71)	13 (87)	0.307	–
BMI, kg/m^2	25 ± 5	27 ± 5	26 ± 3	0.477	–
Current/ex/never smoker, n	0/7/9	12/5/0	8/7/0	<**0.001**	<**0.001**
Pack-years	3 ± 3	36 ± 19	54 ± 22	<**0.001**	<**0.001**
mMRC	0 ± 0	0.71 ± 0.47	1.2 ± 0.56	<**0.001**	<**0.001**
Charlson score	0	0.2 ± 0.4	1.4 ± 0.8	<**0.001**	0.628
CAT score	0.6 ± 0.9	8.9 ± 4.3	10.1 ± 3.1	<**0.001**	<**0.001**
Familiar History**	11 (65)	6 (40)	2 (12)	**0.009**	0.040

* Anova or Wilcoxon or chi-squared test as appropriate. **Familiar history: i.e. positive for respiratory diseases (such as asthma, COPD or interstitial lung disease). BMI: body mass index; CAT: COPD Assessment Test; yrs: years; bold refers to $P < 0.05$ values.

Table 2
Cardiopulmonary exercise testing results.

	Healthy	Symptomatic	COPD*	P Anova**	P Symptomatic *vs.* Healthy
Isotime IC, L	3.30 ± 0 .87	2.50 ± 4.56	2.11 ± 0 .47	<**0.001**	0.215
ΔIC, L	−0.01 ± 0.20	−0.20 ± 0.17	−0.28 ± 0.18	**0.001**	**0.016**
Dynamic Hyperinflation, n (%)	2 (25)	10 (59)	10 (67)	**0.004**	**0.010**
VO_2, %	87 ± 21	69 ± 24	64 ± 17	**0.007**	0.051
VO_2, ml/Kg/min	26.1 ± 6.7	21.7 ± 5.8	16.8 ± 3.9	<**0.001**	**0.034**
AT, % peak VO_2	47 ± 10	44 ± 14	45 ± 13	0.830	-
VE/VCO_2 slope	25.2 ± 4.0	27.5 ± 4.4	30.2 ± 4.6	**0.011**	0.415
VE/VCO_2 intercept	4.4 ± 1.8	4.8 ± 1.9	5.3 ± 2.2	0.422	-
Breathing reserve, %	49 ± 12	36 ± 17	22 ± 17	<**0.001**	0.050

IC: inspiratory capacity; isotime IC: isotime was defined as the minimum endurance time among all the exercise tests; ΔIC: inspiratory capacity at the end of exercise *minus* baseline; dynamic hyperinflation was defined as a decrease of >150 ml in IC compared to resting levels during exercise. VO_2: peak oxygen uptake; AT: anaerobic threshold; VE/VCO_2: ventilatory equivalent for CO_2; for functional data: %: percentage of predicted values; *functional values for COPD patients are reported as post bronchodilator therapy ** Anova or Wilcoxon or chi-squared test as appropriate; bold refers to $P < 0.05$ values.

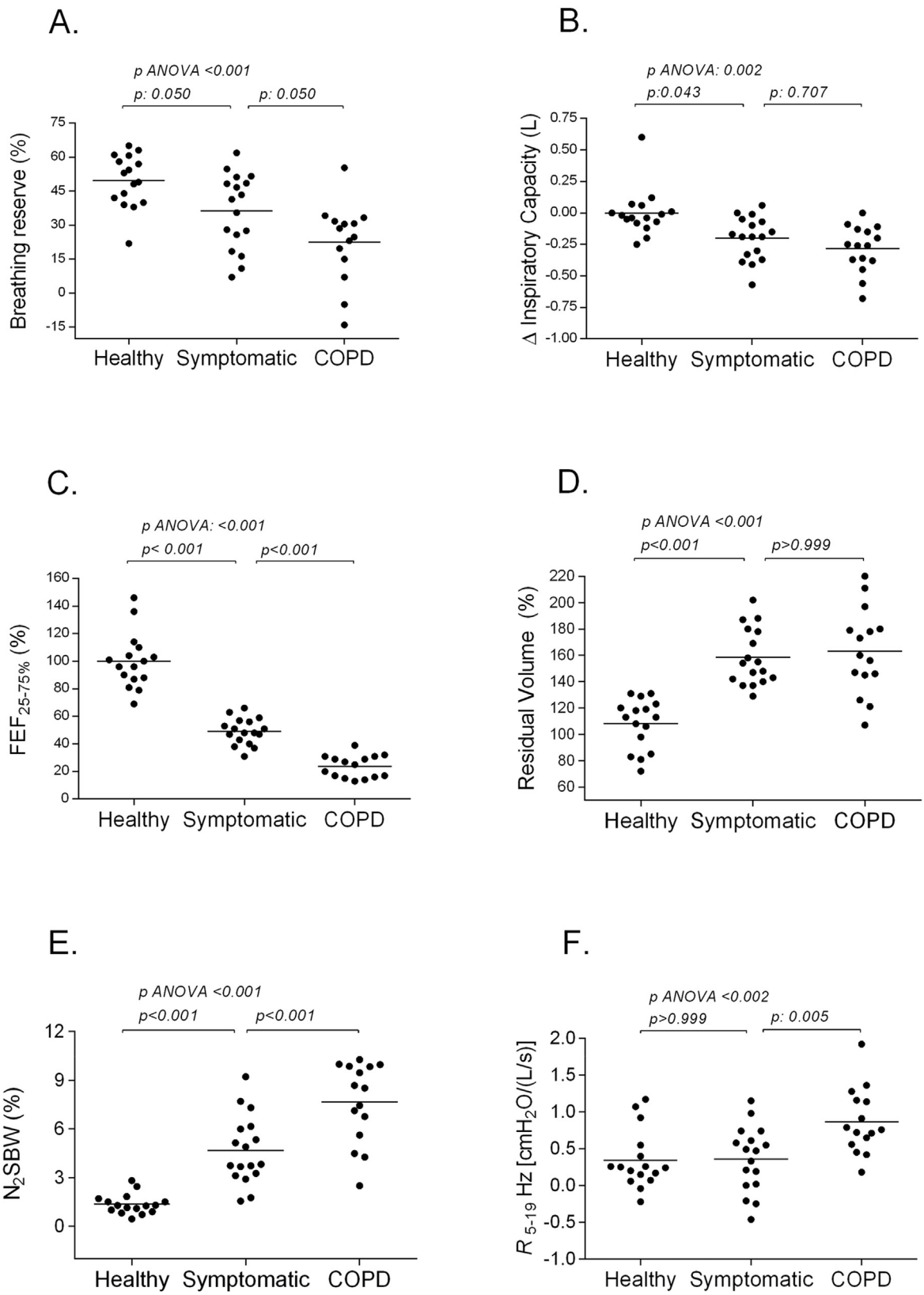

Fig. 1. Differences between the three groups in lung function and cardiopulmonary test results. ΔIC: inspiratory capacity at the end of a steady-state resting baseline *minus* end of exercise. Rrs_{5-19}: difference between Rrs_5 and Rrs_{19}. $FEF_{25-75\%}$: mean forced expiratory flow between 25% and 75% of forced vital capacity. N_2SBW: slope of phase 3.

disease [11]. Indeed, its detection in patients with a high *a priori* risk points towards COPD.

In our study population, the obstructive pattern is characterized by signs of small airways disease and maldistribution of ventilation,

Table 3
Lung volumes and nitrogen single-breath N_2-washout test results.

	Healthy	Symptomatic	COPD*	P Anova**	P Symptomatic *vs.* Healthy
FEV_1, %	108 ± 14	92 ± 15	60 ± 11	<**0.001**	**0.003**
FVC, %	109 ± 15	105 ± 16	85 ± 18	**0.001**	>0.999
SVC, %	107 ± 13	97 ± 13	89 ± 19	**0.007**	0.199
FEV_1/FVC, %	104 ± 5	91 ± 2	75 ± 14	<**0.001**	<**0.001**
FEV_1/SVC, %	101 ± 7	94 ± 9	69 ± 12	<**0.001**	0.148
Reversibility FEV_1, %	–	7±5†	6±4†	–	–
Reversibility FEV_1, ml	–	102 ± 61‡	124 ± 83‡	–	–
IC, %	107 ± 10	109 ± 20	82 ± 17	<**0.001**	>0.999
$FEF_{25-75\%}$, %	100 ± 20	49 ± 9	24 ± 8	<**0.001**	<**0.001**
TGV, %	109 ± 25	128 ± 15	141 ± 26	**0.001**	0.053
RV, %	112 ± 22	158 ± 22	163 ± 32	<**0.001**	<**0.001**
TLC, %	108 ± 11	119 ± 11	117 ± 16	**0.030**	0.033
RV/TLC, %	100 ± 19	129 ± 13	132 ± 16	<**0.001**	<**0.001**
DLCO, %	95 ± 11	84 ± 21	74 ± 20	**0.008**	0.245
DLCO/VA, %	89 ± 10	83 ± 28	70 ± 21	**0.042**	>0.999
VA, %	107 ± 13	99 ± 19	98 ± 12	0.214	–
N_2SBW, %	1.4 ± 0.6	4.7 ± 2.1	7.6 ± 2.5	<**0.001**	<**0.001**
Closing Volume, L	0.721 ± 0.309	0.574 ± 0.366	0.637 ± 0.344	0.472	–
Closing Capacity, L	3.05 ± 1.03	2.72 ± 1.05	2.69 ± 0.81	0.528	–
CC/SVC, %	89 ± 29	80 ± 34	79 ± 33	0.649	–
CC/TLC, %	111 ± 17	109 ± 22	101 ± 14	0.251	–

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SVC: slow vital capacity; reversibility: %: [(post-bronchodilator FEV_1 - pre-bronchodilator FEV_1)/pre-bronchodilator FEV_1] · 100; ml: post-bronchodilator FEV_1 - pre-bronchodilator FEV_1; $FEF_{25-75\%}$, %: mean forced expiratory flow between 25% and 75% of FVC; TGV: thoracic gas volume; RV: residual volume; TLC: total lung capacity; DLCO: lung diffusing for carbon monoxide; CC: closing capacity; for functional data: %: percentage of predicted values; *functional values for COPD patients are reported as post bronchodilatator therapy ** Anova or Wilcoxon or chi-squared test as appropriate; † P = 0.394 for unpaired *t*-test (symptomatic *vs.* COPD patients); ‡ P = 0.332 for unpaired *t*-test (symptomatic *vs.* COPD patients); P < 0.05 in bold.

Table 4
Forced oscillation technique results.

	Healthy	Symptomatic	COPD*	P Anova**	P Symptomatic *vs.* Healthy
Rrs $_5$, %	102 ± 37	101 ± 23	125 ± 39	0.085	–
Rrs $^{\dagger}_5$	2.70 ± 1.07	3.13 ± 1.14	3.57 ± 0.85	0.085	–
Xrs $_5$, %	100 ± 64	90 ± 36	134 ± 72	0.114	–
Xrs $^{\dagger}_5$	−1.10 ± 0 .94	−1.12 ± 0.49	−1.68 ± 0.83	0.074	–
Rrs $_{11}$, %	102 ± 40	103 ± 25	119 ± 38	0.293	–
Rrs $_{11}$, †	2.62 ± 1.02	2.99 ± 1.09	3.20 ± 0 .77	0.263	–
Xrs $_{11}$, %	66 ± 763	370 ± 761	833 ± 1541	0.144	–
Xrs $^{\dagger}_{11}$	−0.06 ± 0.54	−0.16 ± 0.39	−0.66 ± 0.45	**0.002**	>0.999
Rrs $_{19}$, %	90 ± 36	94 ± 26	104 ± 35	0.459	–
Rrs $^{\dagger}_{19}$	2.36 ± 0.86	2.60 ± 1.23	2.70 ± 0.68	0.597	–
Rrs $^{\dagger}_{5\text{-}19}$	0.34 ± 0.39	0.36 ± 0.44	0.86 ± 0.44	**0.002**	>0.999
ΔXrs†	−0.33 ± 0.51	0.04 ± 0.81	0.81 ± 1.42	**0.007**	0.824
Flow limitation, %	0 ± 0	3 ± 9	17 ± 26	**0.008**	>0.999

Rrs and Xrs are tidal breathing values of, respectively, inspiratory resistance and reactance at 5, 11 and 19 Hz; Rrs: resistance; Xrs: reactance; Rrs5-19: difference between Rrs5 and Rrs19; ΔXrs: inspiratory *minus* expiratory Xrs; Flow limitation is defined as the percentage of breaths with ΔXrs >2.53 $cmH_2O/(L/s)$. †: data expressed as $cmH_2O/(L/sec)$. For functional data: %: percentage of predicted values; *functional values for COPD patients are reported as post bronchodilatator therapy ** Anova or Wilcoxon or chi-squared test as appropriate; P < 0.05 in bold.

such as an increase of residual volume and slope of phase 3 of N_2SBW, [21]. The low sensitivity of spirometry in diagnosing isolated small airway disease has been largely demonstrated [22]. The concept of “small airway disease” was thought to represent not only an early phase of the “disease”, but also a step towards overt COPD [23]. Yet, although abnormalities of the small airways have been cross-sectionally associated with chronic obstructive diseases or with disease severity, the evidence that these functional “biomarkers” may predict the time course of the disease is still lacking [21,23].

A concurrent asthmatic condition was excluded by means of a negative medical history and no family history of asthma or atopy, a lack of suggestive symptoms (e.g. nocturnal awakening, cough, wheezing), and was further confirmed by a negative bronchodilator response.

Unexpectedly, we found significant differences in the $FEF_{25-75\%}$ values between the health and the sumptomatic subjects, with only the latter displaying values < 70% (Fig. 1). Given the wide measurement variability and amplitude of normal values, $FEF_{25-75\%}$ is currently considered of limited clinical relevance [5]. $FEF_{25-75\%}$ strongly correlates with FEV_1/FVC, despitein a non-linear fashion, with $FEF_{25-75\%}$ decreasing more steeply than FEV_1/FVC at stages of mild obstruction [24]. The ATS/ERS guidelines on lung function interpretation underline that when FEV_1 and FEV_1/FVC are within the expected range, the clinical significance of abnormalities in flow occurring late in the maximal expiratory flow-volume curve (e.g. $FEF_{25-75\%}$) is limited; however, the same document states that, in the presence of a borderline value of FEV_1/VC, these parameters may suggest the presence of airway obstruction [5]. In contrast with our findings, a previous study performed on a large cohort found that $FEF_{25-75\%}$ does not provide a useful contribution to clinical decision making, [25]. It is likely that in a context of high clinical suspicion for COPD, a negative spirometry is not sufficient for diagnostic definition and second-line pulmonary function tests are required.

In contrast to other studies, we did not find relevant differences

between symptomatic and healthy subjects in DLCO and FOT indexes. Elbehairy et al. showed that FOT was be more sensitive than spirometry in detecting early small airways disease in symptomatic smokers [12]. However, in other populations, such as children with cystic fibrosis, FOT did not demonstrate a high sensitivity in detecting underlying lung disease (defined by CT scan and inflammatory biomarkers); similarly, R_{5-20}, a sensitive parameter for small airway disease, was normal in some smokers with documented airway inflammation [26,27]. The results of our cohort of smokers are,, always intermediate between healthy subject and COPD (see Tables 3 and 4, and Fig. 1). There could be differences which may have failed to reach statistical significance due to the low number of enrolled patients. Elbehairy et al. showed, on average, normal DLCO values in symptomatic smokers (DLCO and DLCO/VA of 93 ± 23, and 99 ± 16, respectively), except for 25% of the subjects with DLCO <80% predicted (we found DLCO<80% in 67% of the symptomatic subjects) [12]. Therefore, we cannot rule out that in patients at risk for COPD, FOT or DLCO evaluation can detect abnormalities in lung mechanical properties; however, our data suggest that, on this ground, body plethysmography or N_2SBW could be more sensitive.

A number of potential limitations of this study deserve discussion. Firstly, as our aim was to propose tests feasible in second level pulmonary outpatient clinics, we focused the analysis on pathophysiological evaluation at rest and during exercise. Indeed, we did not evaluate other methods to detect respiratory impairment, such as imaging, inflammation, and remodeling [28], as most of the latter are invasive, technically demanding and non-standardized, expensive, or use ionizing radiations. Secondly, with the only exception of FEV_1/FVC ratio, we expressed functional data as percentage of predicted values. It is now recognized that the latter is questionable, since its use is associated with bias related to age and height, which are improved if results are expressed as z-scores [29]. However, since the study design was based on group comparison and not on proposing a specific diagnostic cut-off, we expressed the data as percentage of predicted values, approach that is still largely used in clinical practice. In regards to nitrogen washout tests, we chose to use single-breath and not multi-breath technique due to our availability; the latter could be more accurate, yet it is technically demanding and expensive. Finally, we did not address the mechanism of dyspnea by means of the sensory-mechanical relationship during incremental exercise testing, which requires an invasive approach. However, the presence of an impairment of the mechanical properties of the lung combined with dynamic hyperinflation during exercise renders the likelihood of neuromechanical uncoupling very high [30].

5. Conclusions

In presence of respiratory symptoms not fully explained by spirometry, a careful diagnostic approach requires second line tests. Indeed, without a diagnosis it is impossible to prescribe the right therapy, schedule a correct follow-up, and postulate a prognosis. In our study CPET and second line pulmonary function tests revealed an obstructive pattern in symptomatic smokers undetected at spirometry. Whether the natural history of these patients is similar to COPD, and they deserve a similar therapeutic approach is worth investigating. Without a clear demonstration of long-term benefit of bronchodilators in patients with normal spirometry and an obstructive pattern at second-level pulmonary function tests, a strict follow-up appears the current most reasonable approach.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2017.04.006.

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