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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 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, 17 symptomatic smokers, and 15 COPD patients) 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.

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).