Editorial

Evaluation of symptomatic patients without airflow obstruction: back to the future

Jose Luis Lopez-Campos[1,2], Bernardino Alcazar[3]

[1]Unidad Médico-Quirúrgica de Enfermedades Respiratorias, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocio, Universidad de Sevilla, Seville, Spain; [2]CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain; [3]Area Integrada de Gestión de Medicina, Hospital de Alta Resolución de Loja, Agencia Sanitaria Hospital de Poniente, Granada, Spain

Correspondence to: Jose Luis Lopez-Campos. Unidad Médico-Quirúrgica de Enfermedades Respiratorias, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocio, Avda. Manuel Siurot, s/n. 41013 Seville, Spain. Email: lopezcampos@separ.es.

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Throughout recent decades, the concept of chronic obstructive pulmonary disease (COPD) has been evolving from initial clinical observations of single cardinal symptoms and morphological manifestations in the form of chronic bronchitis and emphysema. The 1959 CIBA Guest Symposium defined chronic bronchitis and emphysema in clinical and anatomic terms respectively. Although neither definition used any physiologic criteria, COPD is now defined in functional terms. According to current criteria, COPD is diagnosed in relation to the appearance of an airflow obstruction that is not fully reversible and the history of tobacco exposure (1). Although symptoms help the clinician to suspect the disease (2), the final individual diagnosis relies on a confirmed risk exposure in the medical record and the presence of this non-reversible airway obstruction (1).

In this context, the presence of symptoms considered a diagnostic criterion and the relationship between symptoms and airflow obstruction is a matter of controversy. Traditionally, until very recently, the GOLD document has not been precise on whether symptoms should be a diagnostic criterion for COPD beyond helping patients and clinicians suspect the disease. On the one hand, COPD is a progressive disease with a slow and vague onset, perhaps this is only modified when an acute exacerbation occurs. In COPD, airflow limitation is slowly established and patients are often able to adapt their activities to cope with symptoms. Consequently, they frequently do not perceive symptoms seriously enough until a given threshold is reached, treatment is required, or an acute adverse clinical event occurs. On the other hand, the presence of symptoms in the context of tobacco exposure has been recognized as a key aspect for patient identification. However, there is a lack of relationship between the degree of FEV_1 and the presence of symptoms (3) to a degree that subjects without airflow obstruction can present with respiratory symptoms (4). Interestingly, these subjects with symptoms and no airflow obstruction constitute a challenge for the clinician.

A recent study evaluating the presence of symptoms and exacerbations in patients with history of tobacco exposure but no airflow obstruction has been made available (5). The authors conducted an observational study involving 2,736 subjects. These subjects were divided into four groups according to the presence of symptoms as measured by >10 points in the COPD assessment test (CAT) and the presence of airflow obstruction defined by a post-bronchodilator FEV_1/FVC ratio of <0.7 as well as a fifth control group of subjects who had never smoked. The aim of the study was to evaluate whether those patients with symptoms and preserved lung function had a higher risk of respiratory exacerbations than those who were asymptomatic

with preserved lung function and whether those with symptoms had different findings from the asymptomatic group with respect to other clinical outcomes including the 6-minute walk distance, lung function, or high-resolution computed tomography (HRCT) of the chest. The authors found that respiratory symptoms were present in 50% of subjects with preserved pulmonary function and that these subjects with symptoms and preserved lung function had significantly higher exacerbation rates, greater limitation of activity, slightly lower FEV_1, FVC, and inspiratory capacity, and greater airway wall thickening without emphysema according to HRCT than asymptomatic subjects and controls. The authors conclude that, although these subjects do not meet the current criteria for COPD, they have exacerbations, activity limitation, and evidence of airway disease with an increase in the use of respiratory medications.

In this study, Woodruff *et al*. (5) provide a novel message on subjects with tobacco history and preserved lung function and resume the debate on whether the old GOLD stage 0 "at risk" should be reinstated. These results are relevant and should make us consider different alternatives when evaluating symptomatic smokers with some special considerations. First, there are quite a number of comorbidities that could mimic respiratory symptoms that need to be considered when evaluating subjects exposed to tobacco. Specifically, current smoking, subject-reported physician-diagnosed asthma and musculoskeletal disease have been found to be significantly associated with high CAT scores (6). Additionally, patients with ischemic heart disease, bronchiectasis, anemia, psychiatric disorders, or sleep apnea, among others, could add points in the CAT score for different items of the questionnaire. Therefore, a multi-organ multi-dimensional evaluation of these patients needs to be carried out to confirm the respiratory origin of these symptoms.

Second, the threshold value of 10 in the CAT score used in the study to detect symptomatic cases has been recently challenged by some authors (7). Additionally, the agreement between CAT scores and symptomatic patients as measured by other scales has been called into question (8). In fact, the distribution of CAT values has been recently explored in the four GOLD patient types, indicating that there is a wide distribution of values for all four GOLD patient types (9).

Third, the definition of exacerbation solely based on the use of antibiotics or systemic glucocorticoids or an acute health care utilization event is a standard in different trials. However, some of the above-mentioned comorbidities could also have exacerbations of their own conditions that would fit in this definition, which is part of the current debate on the definition of exacerbation (10). In fact, it is interesting to see that an episode such as an exacerbation was superior in the group with preserved lung function and symptoms compared to patients with obstruction without symptoms. This highlights the complex relationship between lung function, symptoms and exacerbation frequency and justifies an approach that considers all these aspects separately in clinical evaluation (1). COPD should be evaluated and understood more comprehensively in order to understand what pathophysiological processes occur in these patients in order to obtain more frequent requests for healthcare.

Despite these considerations, Woodruff *et al*. (5) indicate that their findings are real after adjusting for confounders. If this associations were true, this would then raise the question of whether the clinical definition of COPD should be adjusted or whether a new entity that includes the population of patients with smoking-related chronic pulmonary disease who do not meet the standard criteria for airway obstruction should be considered (11). In fact, there are cases in the literature with previous tobacco exposure and no obstruction but with emphysematous lesions or a decreased diffusing capacity in lung function testing (12). The COPDGene cohort recently characterized the clinical, functional, and radiographic features of these cases (4) who accounted for 9% of the cohort. Similar to the study by Woodruff *et al*. (5), these patients exhibited increased airway wall thickness, decreased gas trapping and bronchodilator responsiveness compared to subjects with COPD with a wide range of lung function impairment, BMI, and percentage of total lung emphysema. However, until now, the scientific community has not reached a consensus on how to define these cases. A previous attempt was made in the first editions of the GOLD document in which it was called COPD stage zero to define patients with normal spirometry and chronic symptoms, e.g., cough and sputum production. This stage was called "at risk" in the understanding that these patients would be at risk of progressing to stage I (13). Notably, GOLD 2006 eliminated this stage, no longer including it as a stage of COPD since there was incomplete evidence that the individuals who met the definition of "at risk" necessarily progressed to stage I (14).

In light of these findings, this clinical challenge may pose three relevant questions. First, if COPD diagnosis should continue to be a functional disease, and, if so, if spirometry should continue to be the test used to examine

airway impairment as currently recommended (15). On the one hand, due to the slow progression of the disease, the diagnosis of COPD is often delayed until more severe airflow obstruction is detected. Accordingly, the perception of symptoms by the patient may be delayed. Additionally, the presence of symptoms has been shown not to be a reliable indicator of disease progression (16). On the other hand, Woodruff *et al*. (5) suggest that patients without a disease detectable by spirometry have symptoms before a spirometry can detect a significant airflow obstruction. Therefore, the question arises whether these symptomatic patients should be considered COPD cases and what would then be the diagnostic criteria if spirometry is not able to detect them. Notably, other more physiological measurements of lung function may provide more relevant information at the earliest stages of the disease (17). Alternatively, other objective measurements including radiological manifestations (e.g., airway involvement or degree of emphysema) or the identification of biomarkers would also be an approach to be developed in the future (12).

Second, the need for screening in the general population becomes another source of debate. Although population screening is not recommended in the general population (18), targeted case finding may be an alternative to detect patients who may be at increased risk for COPD (19). In particular, several questionnaires have been evaluated to have a role in identification of the disease (20). In this scenario, it follows that a questionnaire detecting COPD with no obstruction in the spirometry poses a challenge for the clinician.

Finally, the last challenge is to decide whether these non-obstructive symptomatic patients require treatment, either pharmacological or non-pharmacological in the form of exercise training or bronchodilators. Disgracefully, there are no clinical trials evaluating the impact of the different available therapies on these patients. Future research will need to shed some light on this patient type to identify proper diagnostic criteria and select the best available therapy. Remembering the 1985 American science-fiction adventure comedy film *Back to the Future*, in the future we will need to go back to considering these patients and allocating them in a determined stage of the disease which will help to consider them as special populations and develop clinical trials that allow us to decide on the best treatment.

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Footnote

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