Is it time to move beyond the “0” in early COPD?

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Obstruction may not be present in early COPD <http://ow.ly/TqC3E>

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally [1] and is the focus of primary and tertiary prevention programmes [2, 3]. Primary prevention has focused on reduction of risk factors, such as tobacco smoke exposure [4] whereas tertiary prevention has focused on reducing exacerbations or improving symptoms among patients with established disease [5]. Missing from prevention approaches are secondary prevention strategies that find disease because it becomes clinically apparent. The US Preventive Services has recommended that spirometry (which detects obstruction) not be used to screen for COPD [6] and recommendation was confirmed in a guideline document from the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society and the European Respiratory Society [7]. The reasons for this recommendation are complex but one of the factors is that, while spirometry can detect mild airflow limitation, not all people with this limitation go on to develop more severe airflow limitation and its clinical consequences or, stated more simply, early COPD may not be the same as mild COPD.

The topic of “early COPD” is the focus of a recent review by RENNARD and DRUMMOND [8]. They recognise that COPD is a heterogeneous collection of different pathophysiological processes that result in a patient developing airflow limitation. Some of these processes include poor lung development (compromised intrauterine development, reduced lung growth in childhood), excess lung damage (cigarette smoking, air pollution, infections), airway remodelling (asthma, bronchitis), and deficient lung maintenance or repair (cigarette smoking, starvation, ageing) [8]. With different processes affecting the development and progression of COPD, one can see that a single means of assessing COPD (and early COPD) would be inadequate. Most studies and interventions focused on the detection of early COPD have used spirometry [9–11]. Other measures, such as lung volumes, diffusion capacity of the lung for carbon monoxide (*DLCO*), exercise capacity, imaging, activity measures, or health status assessments, may also have an important role [8].

HARVEY *et al.* [12] in this edition of the *European Respiratory Journal*, followed a cohort of smokers with normal spirometry for up to 13 years and found that among those with a low *DLCO* (<80% predicted), 10 (22%) out of 46 developed obstruction (forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) <0.70), whereas among those with normal *DLCO* (≥80%), only two (3%) out of 59 developed obstruction. Only two out of 46 of patients in the former group and one out of 59 in the latter group had an FEV₁ that was less than 80% at the end of follow-up (figures 1 and 2 in the article). Interestingly, among the subset of patients who had CT scans available, there was no difference in the percentage of emphysema between the low *DLCO* and normal *DLCO* groups (supplemental figure 2 alongside the article) [12].

They used as an endpoint the development of obstruction using the fixed ratio of FEV₁/FVC, which is a controversial area in COPD [13]. Most of the patients developing obstruction would be classified as having

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stage 1 obstruction, which some argue does not represent disease [14]. Also, the main predictor used, a DLCO of <80%, would not be considered abnormal for many patients in a number of interpretative strategies [15]. The data presented, however, are compelling and appear to represent patients with one type of early COPD.

This work raises additional questions. Does obstruction, the “O” in COPD, always need to be present in patients with early and more advanced stages of disease attributed to cigarette smoking and inhaled noxious agents? Does emphysema in the absence of obstruction represent COPD? Does impaired diffusing capacity in otherwise healthy people who later develop obstruction represent an early phenotype (or endotype) [16] of COPD?

As REGAN *et al.* [17] have demonstrated in the COPD Gene cohort, smokers with normal spirometry (a group previously called GOLD Stage 0 when “symptoms” are present) have significantly worse quality of life, 6 min walk distance, and 42% had emphysema or airway thickening on chest CT scan [17]. In a single centre analysis of patients who had a chest CT scan for evaluation of the lungs, 274 of 2125 patients had more than 5% emphysema. In that study, spirometry using the lower limit of normal failed to identify 13.9% of patients with emphysema and using the fixed ratio of FEV₁/FVC <70% failed to identify 6.9% of patients with emphysema [18].

In 1958, Dr Charles Fletcher chaired a symposium to see whether British investigators could “agree upon provisional definitions, classifications and terminology” for chronic respiratory disease. The report focused on the interaction between chronic or recurrent excessive secretion of bronchial mucus, intermittent obstruction to bronchial air flow, and persistent obstruction to bronchial air flow [19]. Interestingly, that report noted that abnormal lung function in the assessment of chronic lung disease needed to consider ventilatory function, alveolar-capillary function, and pulmonary circulatory function. Although the term “COPD” did not appear in this document, it provided the basis [20] for subsequent guidelines [21–23] that focused on COPD. Central to these guidelines is the use of spirometry, a measurement of ventilatory function, without considering other factors that lead to the development and progression of COPD.

Now, nearly 60 years following that symposium, we are revisiting how the disease processes comprising “COPD” are best defined, with a special focus on secondary prevention strategies. We believe that a growing body of evidence, including the paper by HARVEY *et al.* [12] in this journal, suggests that airflow limitation alone is insufficient to convey the full burden of pathophysiology in early obstructive lung disease.

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