

Editorials

The heterogeneity of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in adults and has important health economic consequences. Despite being such an important cause of health impairment,¹ the diagnosis of COPD is often made relatively late in the natural history of the disorder when there is already an appreciable fall in the forced expiratory volume in one second (FEV₁) and symptomatic deterioration, as the early stages of the disease are relatively asymptomatic. COPD is formally defined by spirometric criteria according to the British Thoracic Society (BTS) guidelines on the management of COPD as a chronic slowly progressive disorder characterised by largely fixed airways obstruction (FEV₁ <80% predicted and FEV₁/FVC ratio of <70% predicted).² However, we now know that COPD is a largely heterogeneous condition, consisting of a number of pathological processes whose effects are modified by varied host susceptibility.³ Some patients present with daily symptoms of cough and sputum production, suggestive predominantly of chronic airway inflammatory processes, that can make the differential diagnosis from bronchiectasis difficult in clinical practice. Others complain predominantly of dyspnoea caused by the hyperinflation associated with the disease and may have a different natural history from those producing sputum. Early studies showed little association between the hypersecretory and obstructive forms of COPD,⁴ but other studies have shown positive relationships between chronic mucus hypersecretion and decline in FEV₁.⁵ Knowledge of the natural history of these different processes and methods of diagnosis of COPD is still generally poor, making early detection of COPD patients problematical and identification of those who may be most susceptible to exacerbation and hospital admission particularly difficult.

Most patients who present with COPD in secondary care have a known diagnosis of moderate to severe COPD and spirometric parameters are usually measured either in the outpatient clinic or during a hospital admission. Although much recent emphasis has been placed on COPD in secondary care in view of the consequences of hospital admission, most patients with COPD are diagnosed and managed in primary care where many patients have mild COPD and diagnostic spirometric measurements are still limited in their use. Thus, the diagnosis of COPD in primary care will be mainly determined on clinical grounds rather than on formal spirometric criteria. As smoking cessation is currently the only intervention that can modify the natural history of COPD,⁶ there is an urgency for early recognition and management of COPD in primary care to stop further irreversible changes in lung function.

Indeed, many patients in primary care will only come to attention when seen with an exacerbation. Thus, the paper in this issue of *Thorax* by O'Brien and colleagues is particularly welcome as it is the first detailed study of the

characterisation of COPD patients presenting in primary care.⁷ The study describes a detailed evaluation of 110 patients who presented to primary care with a diagnosis of an acute exacerbation of COPD and who were later, after two months when clinically stable, investigated with full lung function and, most interestingly, with CT scanning. The findings of this paper suggest some novel characteristics of this important disease and challenge some of the accepted definitions of COPD. The results showed that 30% of the patients with a diagnosis of COPD had a normal FEV₁ (>80% predicted) when stable, though nearly half of these patients had a reduced FEV₁/FVC ratio which suggests that airflow obstruction was indeed present, though the criteria in the BTS COPD guidelines were not fulfilled. Thus, future guidelines for the management of COPD may have to revise their definitions to encompass patients with early COPD, as in this paper. This study also emphasises the importance of measuring the vital capacity in these patients. Only 5% of the cohort showed a significant bronchodilator response, suggesting that a diagnosis of asthma was not a prominent feature in this study. However, a limitation of the study is that patients were only included if they had an exacerbation, and some COPD patients with progressive airflow obstruction may have only infrequent exacerbations and would not have been part of this particular cohort.¹

High resolution CT (HRCT) scanning is useful in the diagnosis and assessment of a number of lung parenchymal diseases and is the most sensitive method for detecting emphysema. CT scanning is now the investigation of choice in the diagnosis of bronchiectasis with accepted diagnostic criteria.⁸⁻¹⁰ Two previous studies have shown that the incidence of bronchiectasis on CT scanning is high in patients with chronic cough and sputum production, though these studies included mainly non-smokers referred for investigation of cough and sputum production.^{11 12} An important finding in the study reported by O'Brien and colleagues was that HRCT evidence of bronchiectasis was present in 29% of the COPD patients evaluated. The patients with bronchiectasis were clinically indistinguishable from the remainder of the COPD group, though the clinical significance of the high incidence of bronchiectasis in a cohort of patients with COPD is not understood.

Some patients with COPD are prone to frequent exacerbations that are an important cause of morbidity, mortality, hospital admission, and reduction in health status.^{1 13 14} Patients with a history of frequent exacerbations have increased airway inflammatory markers and this may lead to deterioration in lung function, though there is no current evidence that the physiological effects of exacerbations contribute to the decline in lung function characteristic of COPD. Factors which predict frequent exacerbations were the number of exacerbations in the previous year and a

history of bronchitic symptoms (cough and sputum production), though lung function was not related.¹ Thus, it is possible that patients with frequent exacerbations may have some associated bronchiectasis, especially as frequent exacerbations are associated with baseline cough and sputum production. On the other hand, patients with infrequent exacerbations may have a greater predominance of emphysema on CT scanning. Thus, CT scanning may enable us to differentiate between patients with frequent and infrequent exacerbations, though this hypothesis requires testing. Could the COPD patient group described by O'Brien and colleagues with bronchiectasis be more susceptible to the development of exacerbations? The findings of a high incidence of bronchiectasis in this study could reflect the entry criteria since all patients presented with an exacerbation and thus many could fall into the frequent exacerbation group. However, the results of this study suggest that CT scanning may play an important part in defining further the nature of COPD and evaluating whether this subgroup with bronchiectasis is more susceptible to exacerbations or has a worse prognosis.

Another interesting finding in this study is the presence of a significant co-morbidity in this patient population from primary care. In 40% of the cohort there was evidence of vascular disease or diabetes and 14% had more than one co-morbid condition (usually hypertension with coronary artery disease). Associations that are independent of the effects of cigarette smoking have been reported between the risk of coronary artery disease and symptoms of chronic cough and sputum.^{15,16} Raised plasma fibrinogen levels are an important predictor of increased cardiovascular risk and patients with COPD have been shown to have increased stable plasma fibrinogen levels that rise further with an exacerbation.¹⁷ This may explain the increase in cardiovascular risk in patients with COPD found in epidemiological studies. Thus, early diagnosis of COPD may be important, not only to characterise the patients who may develop a progressive decline in lung function, but also to identify a group that have an increased cardiovascular risk and to implement effective smoking cessation programmes at an early stage of the disease.

Recent data have suggested that COPD is a complex and heterogeneous disorder with a number of different pathological processes leading to recognition of subgroups that may have their own characteristics and natural history. Do COPD patients with bronchiectasis form a worse prognostic group? Advances in HRCT scanning of the chest may be particularly useful in defining some of these variants and further research is required on this subject. With increasing

knowledge of the mechanisms of airway inflammatory changes in COPD, definitions of COPD will need to be reviewed, especially as there is a need for emphasis on the early diagnosis in primary care. The availability of methodology to characterise COPD more carefully will lead to a revision of some of the original concepts of the natural history of COPD. This will at last enable us to make an important impact on the reduction of exacerbation frequency and the associated improvement in health status.

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