The HRCT scan pursuing real life pathology

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HRCT scanning brings a new dimension to studies of COPD

The pathogenesis of chronic obstructive pulmonary disease (COPD) is widely considered to be the result of uncontrolled pulmonary inflammation. This is based on the original concept of a protease/antiprotease imbalance leading to peripheral tissue destruction and the development of emphysema. The premature development of emphysema in \( \alpha_1 \)-antitrypsin deficiency gave rise to this hypothesis and led to an increasing field of research in the 1970s investigating the inflammation in emphysema using bronchoalveolar lavage. In addition, a series of in vitro experiments investigated the ability of enzymes to produce emphysema-like lesions and its prevention by proteinase inhibitors. More recently the smoking mouse and a series of gene knock-out and transgenic animals has explored not only the role of proteinases and inflammatory cells, but also proinflammatory cytokines, adhesion molecules, and growth factors in the development of emphysema.

The study of upper airway secretions has indicated that inflammation is also present at this site, and several studies have demonstrated a proteinase/antiproteinase imbalance that is likely to influence the nature of airways disease, including development of bronchiectasis, mucus hypersecretion, and disturbances of mucociliary clearance. However, many patients do not expectorate spontaneously, and hence the process of sputum induction was applied to obtain samples from the upper airways in patients with COPD, as defined by the presence of airways obstruction. These studies have led to a change in direction concerning the important cellular and inflammatory proteins that are key to the pathogenesis of COPD.

However, the research field has lost sight of the fact that COPD is a multi-component multi-compartment disease. The key defining feature is airflow obstruction that is largely irreversible. This physiological abnormality may reflect obliteration of the small airways by oedema, mucus plugging and fibrosis, as well as collapse on expiration due to loss of supporting elastin attachments which is a feature of emphysema. Whereas the small airway mucus, oedema and fibrosis represent inflammation in the airways, the loss of connective tissue supporting structures is related to interstitial inflammation and the development of emphysema.

It is possible with pathological specimens to relate the emphysema to inflammation in cross sectional studies, but the ability to relate structural changes to inflammation in vivo and, in particular, in longitudinal studies has been impossible to date.

The development of HRCT scanners has brought a new dimension to studies of COPD. The scanner acts as a densitometer and reconstruction provides a visual image that enables the viewer to identify low attenuation areas consistent with the loss of lung tissue that accompanies emphysema. In addition, the contrast between the solid bronchial walls and the air within the lumen enables the bronchi to be visualised with a diameter as low as 1 mm. The pattern of low density areas enables a diagnosis of centrilobular and panacinar emphysema to be made with reasonable accuracy (fig 1). Furthermore, the presence of dilated airways is now the gold standard for the diagnosis of bronchiectasis. When such studies are applied to patients with a diagnosis of COPD, it is clear that bronchiectasis is common (approximately 25% of patients) but that, even in severe airflow obstruction, emphysema is often not visually identified. A further advantage of HRCT scanning is that densitometric analysis allows a quantitative measure of emphysema to be made, and this matches well with the macroscopic and microscopic assessment of pathological specimens. This methodology therefore provides a real opportunity to follow the progression of emphysema in vivo.

However, the density of lung tissue is not only influenced by the presence of emphysema but also by the level of inspiration. Thus, the quantification of emphysema can be incorrectly estimated by the density unless the level of inspiration is controlled. This is a particular problem on the expiratory film when abnormalities in the small airways result in premature closure and hence air trapping. The retained air remains hypodense and can become more apparent as the emptying normal lung that surrounds it becomes more dense. The degree of air trapping may thus be independent of the presence of emphysema and, for this reason, full inspiratory films are best to quantify the emphysematous pathology.

Despite this apparent problem, the expiratory scan can be more informative about the pathological processes taking place than the inspiratory scan. In the paper by O’Donnell and colleagues in this issue of Thorax, the authors have used parameters derived from the inspiratory and expiratory HRCT scans to assess the relationship between peripheral airway dysfunction and physiological abnormalities and airway neutrophilia in COPD. The patients studied had a wide range of forced expiratory volume in 1 second (FEV1) abnormality. By definition, this shows progressive impairment within broad groups of the GOLD staging. Similarly, the flow rate at 50% expiration (MEF50%) showed progressive impairment across the groups, as did...
the carbon monoxide transfer factor (TlCO, a measure of gas distribution and uptake). On the other hand, the carbon monoxide transfer coefficient (Kco), which is a more direct measure of loss of alveolar gas exchanging surface (emphysema), showed no progressive impairment from stage 0 to stage II–IV, which is consistent with the emphysema being reported as minimal to extensive even in the severe group. The authors analysed the HRCT scan in two ways—firstly, the expiratory to inspiratory lung density ratio which reflects the degree of air trapping and hence small airways disease and, secondly, the proportion of low density areas on the inspiratory scans which reflects the amount of emphysematous tissue. Using the latter data, there was no correlation with Kco which is at variance with other studies of patients with emphysema.11,12 This again suggests that the results are influenced by the mild degree of emphysema seen in many of the patients. Indeed, the average proportion of low density areas seen in the three groups on the inspiratory scan (5.8–11.4% in table 1 of the paper10) confirms this to be the case. Of particular importance is the failure of the neutrophil counts to correlate with the degree of air trapping and, hence small airways pathology. It is therefore more critical that future studies should clarify the phenotype of the patients being studied so that conceptual quantum leaps in pathophysiology are not made. Standardisation of algorithms used in the CT scan and more radiopathological comparisons and analytical techniques offer a real opportunity to study the pathophysiological processes involved in structural changes within the lung and, more importantly, their progression or response to treatment.


There are a number of reasons for the discrepancy between the studies conducted on this subject. Firstly, smoking is a very significant confounder in the development of emphysema which is almost impossible to control for. Secondly, many studies have been subject to various types of bias, particularly selection bias. Thirdly, only a few studies have been sufficiently large to produce a significant result and very few studies have been population based. Finally, the phenotypic appearance of the Pi MZ genotype may be heterogenic.

In the studies of a causal relationship of a risk factor (Pi MZ genotype) and the development of a disease (COPD) there are two types of designs: case-control studies and cohort studies. Cohort studies can be divided into cross sectional studies and follow up studies. In case-control studies the researchers identify a group with COPD, find a proper control group without the disease, and compare the prevalence of the Pi MZ genotype between the two

Pi MZ and COPD

Pi MZ and COPD: will we ever know?

N Seersholm

Based on the current evidence, there is no reason to believe that Pi MZ individuals have an increased risk of developing lung disease as long as they do not smoke

I s Pi MZ a risk factor for the development of chronic obstructive pulmonary disease (COPD)? That is the question many authors have tried to answer during the last decades, but the results of published studies are still conflicting.

A very high percentage of patients with COPD have been smokers, but not all smokers develop COPD. There must be other contributing factors and, with a Pi MZ prevalence of 3–5% in many Western countries, it is relevant to determine whether this genotype is an additional risk factor for COPD.1 Furthermore, if a dose-response relation exists, it is biologically plausible since plasma levels of α1-antitrypsin (AAT) are reduced to about 60% in Pi MZ subjects compared with those with the normal Pi MM genotype, and Pi Z individuals with very low levels of AAT have a significantly increased risk for emphysema.