Eur Respir J 2008; 31: 913–914
DOI: 10.1183/09031936.00026208


EDITORIAL

# Remodelling of peripheral lung tissue in COPD

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Chronic obstructive pulmonary disease (COPD) is a major worldwide public health problem caused by the inhalation of toxic particles and gases primarily as a result of tobacco smoking [1]. In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) assembled an international panel of experts to develop, continuously monitor and upgrade guidelines for diagnosis of the disease, classification of its severity and the optimum management of COPD [1, 2]. The criteria for diagnosis and severity of COPD are based on measurement of post-bronchodilator forced expiratory volume in one second ($FEV_1$) and its ratio to forced vital capacity (FVC) [1, 2]. Because these measurements reflect the time constant for lung emptying, they detect the combined effect of resistance offered by the airways and lung compliance, which determines the elastic force required to drive air out of the lungs. However, these measurements cannot separate one from the other. The lesions at both the site of airway obstruction and emphysematous destruction contain a persistent infiltration of inflammatory immune cells that becomes more extensive and severe as COPD progresses [3–6]. This inflammatory immune response is inextricably linked to a repair and remodelling process that thickens the walls and narrows the lumen of small conducting airways and causes emphysematous destruction of gas-exchanging tissue [6, 7]. Although the lungs from most patients with COPD have a mixture of lesions, studies based on high-resolution computed tomography indicate that they can be separated into phenotypes in which either airway obstruction or emphysematous destruction predominate [8, 9].

In the current issue of the *European Respiratory Journal*, BLACK *et al.* [10] provide new information concerning the elastin content at these two sites, based on the examination of tumour-free portions of lung specimens removed from patients with cancer. The results of BLACK *et al.* [10] indicate that a reduction in tissue elastin content is a common denominator of both the small airway obstructive and emphysematous destructive lesions, and they conclude that the loss of elastin in the airways contributes to airflow obstruction in COPD. This conclusion is unfortunate because the measurements of $FEV_1$ and $FEV_1$/FVC cannot separate airway resistance from lung compliance, making ''airflow limitation'' a better choice of words. That said, their observation that elastin degradation is present in both small airways and gas-exchanging tissue is both new and important.

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STATEMENT OF INTEREST: A statement of interest for J.C. Hogg can be found at www.erj.ersjournals.com/misc/statements.shtml

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Several previous studies have attempted to assess changes in elastin content of the lungs with varying results. Biochemical approaches necessarily include the elastin present in the vasculature, conducting airways, alveolar walls and pleural surfaces [11]. Moreover, the form of elastic fibres in small airways and alveolar walls is quite different. In alveolar walls, single elastic fibres encircle alveolar openings and are thus prominent at the tips of alveolar septae, visualised in cross-section. Their thickness is nearly the same as the entire thickness of the alveolar wall, usually separated from the airspace only by the thin cytoplasm of alveolar type I epithelial cells. In large airways containing cartilage, bundles of elastic fibres extend parallel to the long axis of the airway and may also occur in oblique arrays in the adventitial layer. In smaller bronchi and bronchioles, the fibres are embedded in the airway wall. BLACK *et al.* [10] avoided these difficulties by using a semi-quantitative histological analysis to estimate the elastin content in both small airways and alveolar walls, although one might quibble that for practical reasons BLACK *et al.* [10] were unable to obtain a reference volume that would have turned their volume fractions into real volumes [12]. The analysis by BLACK *et al.* [10] showed that elastin was reduced in both locations and that these reductions were associated both with each other and with the decline in $FEV_1$ and $FEV_1$/FVC. This strongly suggests that the destruction of elastin in COPD is global in nature and not limited to gas-exchanging tissue, and these data are important for several reasons.

In distensible tissues containing both elastin and collagen, the elastic component controls the rate of distension as force, is applied and confers the passive recoil of the tissue in returning to its resting length after the force is removed. Collagen, in contrast, behaves like string in that it is easily stretched to its resting length and then vigorously resists further lengthening. Estimates of the pressure–volume characteristic of centilobular emphysematous lesions are consistent with loss of elastin in that they are inflated to ~60% of their full capacity at the low distending pressures present near minimal lung volume and only slowly increase from 60–100% of their full volume as the lung is inflated to total lung capacity [13]. The reduction in elastin content in emphysematous regions of the lung demonstrated by BLACK *et al.* [10] is entirely consistent with the behaviour of the centrilobular lesions. Moreover, their simultaneous demonstration of reduced elastin content in small airways tissue raises the question as to whether the airways behave in a similar fashion. In one of the first descriptions of the centrilobular form of emphysema, LEOPOLD and GOUGH [4] reported data from serial histological sections of 90 individual centrilobular lesions. These data showed: that the terminal bronchioles supplying these lesions were infiltrated with lymphocytes and plasma cells in 86% (78 out of 90) of the lesions examined; and that this inflammatory infiltration was associated

with the deposition of connective tissue, which thickened walls and narrowed lumens in 60% (54 out of 90) of these airways. Although no one that we are aware of has repeated this study, others have shown that the small bronchi and bronchioles <2 mm in diameter also have thickened airway walls [5, 6]. If they behaved like centrilobular emphysematous lesions, one would expect their lumens to nearly fully dilate and have a low resistance at minimal lung volume. With lung inflation, this resistance should fall continuously until total lung capacity is reached as small increases in the radius of a tube raised to the fourth power sharply reduce the resistance to flow. At least three laboratories have shown that these smaller airways are the major site of resistance in COPD and that this resistance is highest near minimal lung volume [14–16]. This resistance falls only slightly in the mid-volume range and then begins to increase again near the higher lung volumes [14–16], which is more consistent with a fixed obstruction due to other changes in the airway wall.

An alternative explanation for the reduced elastic fibre content as a percentage of total tissue in the airways is that the degradation of elastin is accompanied by increases in the other components of the airway walls that reduce lumen diameter, restrict its dilatation with lung inflation and cause the lumen to narrow as the airways lengthen at higher lung volumes. Some years ago, MATSUBA and THURLBECK [17] showed dense deposition of collagen around the smaller airways in lungs from patients with severe emphysema; more recent work has shown that the epithelium, lamina propria and adventitial compartments all participate in airway wall thickening [6]. However, the mechanism(s) that allows the airways to thicken within regions of the lung undergoing emphysematous destruction remains a puzzle that needs to be solved. A perfect understanding of how this occurs could lead to the identification of better targets for treatment in both types of lesion. In persistently damaged tissue, the deposition of connective tissue matrix is controlled by the balance between its synthesis and degradation within the damaged area [18]. Therefore, the pre-terminal and terminal airways might remain thickened when the respiratory bronchioles undergo emphysematous destruction because this balance shifts to favour degradation as the chronic inflammatory process spreads into the gas-exchanging tissue from the conducting airways.

By showing that the destruction of elastin is global in nature, BLACK *et al.* [10] introduce new data that may help explain why the bronchioles are initially spared but then disappear with destruction of the entire lobules and the coalescence of many destroyed lobules to form larger emphysematous lesions. In our view, this means that the BLACK *et al.* [10] have not simply shot an arrow into an empty canvas and painted a target around it, they have carefully aimed their arrow to pass through difficult terrain and hit an important target that opens up new and important questions about lung remodelling in chronic obstructive pulmonary disease.

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