Ageing, smoking and oxidative stress

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The complex relationship between age, oxidative stress, duration of smoking cessation, and inflammatory markers

Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death worldwide and further increases in its prevalence and mortality are expected in the coming decades.¹ Continued exposure to tobacco promotes a more rapid decline in lung function and, if exposure is stopped, the disease may still progress due to ageing and persistence of inflammation. The paper by Nagai *et al*² in this issue of *Thorax* adds to the growing body of evidence about damage from oxidative stress due to cigarette smoking. Changes can persist even after the last cigarette is extinguished. The effects are more noticeable in older smokers because of long term exposure to toxic gases and particles as they concurrently age. Oxidised glutathione associated with excessive protein carbonylation accumulates in the lungs of older smokers, raising the possibility that antioxidant defences could be overwhelmed.

The lungs are exposed continuously to oxidants generated either endogenously from phagocytes and other cell types or exogenously from air pollutants or cigarette smoke. Cigarette smoke contains 10¹⁷ oxidant molecules per puff.³ The oxidants in cigarette smoke cause lung injury by a number of mechanisms including the depletion of glutathione and other antioxidants, the initiation of redox cycling mechanisms, enhancement of the respiratory burst in neutrophils and macrophages, inactivation of protease inhibitors such as α_1 -antitrypsin inhibitor, and direct damage to lipids, nucleic acids and proteins.⁴ There is considerable evidence that the oxidative burden is increased in the lungs of patients with COPD and may be involved in the pathogenetic processes in the lung and in the systemic manifestations of weight loss and muscle dysfunction.³

Oxidative stress is measured in several different ways including direct measurements of oxidative burden via nitric oxide in exhaled breath, responses to oxidative stress via antioxidant enzymes in blood, sputum and bronchoalveolar lavage (BAL) fluid, or the effects of oxidative stress on target molecules.³ Antioxidant strategies in

smoking related airway disease and antioxidant enzymes have recently been reviewed.⁵ Nagai and co-workers chose to measure the effects of oxidative stress on protein target molecules via protein carbonyls in BAL fluid. The oxidation of proteins may play an important role in the pathogenesis of chronic inflammatory lung disease, as higher levels are measured in diseases such as cystic fibrosis, asbestosis, and idiopathic pulmonary fibrosis compared with healthy controls. The proteins most susceptible to oxidation are albumin, surfactant proteins A and D (which are also decreased in BAL fluid of long term smokers), and α_1 -antitrypsin. In some studies of BAL fluid the extent of protein oxidation correlates with neutrophil counts, but that was not the case here.

In this study older smokers with long term smoking histories had excessive protein carbonyls and accumulated glutathione disulfide (GSSG) in BAL fluid. The authors claim that, for the first time, the oxidation of albumin—the most abundant protein in the BAL fluid—has been shown to account for the excessive total protein carbonylation. Thus, the possibility that lung antioxidant defences might be overwhelmed is considered but further studies are necessary. Also of interest was the observation that ageing alone did not affect the level of protein carbonyls, total glutathione, or GSSG in BAL fluid. Ageing plus smoking is necessary, as younger current smokers have demonstrated lower levels of oxidative stress.

Since the oxidant/antioxidant imbalance is implicated in the pathogenesis of emphysema, the lack of an effect of emphysema in this study is surprising. The emerging distinctions between asymptomatic smokers and those with COPD, and between those with mild and severe obstructive disease, highlight a limitation of the paper by Nagai *et al*—namely, that only a small percentage had COPD and it was mild. The baseline forced expiratory volume in 1 second (FEV₁) was normal and there was little radiographic evidence of COPD. These observations on oxidative stress cannot

therefore be extended to COPD at this time. While oxidative stress is increased in COPD, its precise role in the progression of the disease is under intense study. Oxidative stress enhances inflammation. As mentioned, there may be differences in inflammation distinguishing those smokers who develop COPD and those who do not. In addition, there appears to be a cascade of events that takes place during progression from mild to severe disease.⁶ T lymphocytes (particularly CD8+ cells and macrophages) predominate in the lungs of healthy smokers and those with mild COPD while neutrophils predominate in those with severe disease. It would be interesting to replicate these observations on oxidative stress in older smokers in a study of patients with COPD of varying stages of severity according to the Global Health Initiative on Obstructive Lung disease (GOLD).

The level of total protein carbonyls in BAL fluid was raised for 1 year not only in older current smokers but also in older former smokers. This adds to the growing body of information that the damage due to smoking persists, especially in those with established COPD. Clinical and pathophysiological changes occurring after cessation of smoking are variable and quite complex. While improvement in symptoms, pulmonary function, airway hyperresponsiveness, and all cause mortality are expected, many ex-smokers—especially those who are older with COPD—are disappointed by their lack of progress and/or continued deterioration once they have discontinued smoking. Recently, research into the pathogenesis of COPD has begun to address changes after cessation of smoking. For example, it is now apparent that, in some individuals with COPD, persistent airways inflammation,⁷ increased airway epithelial and T cell apoptosis⁸ and, in this study, oxidative stress remain for up to 12 months or more after smoking cessation. Potential explanations for these changes in COPD include persistent inflammation from infectious colonisation with bacteria or *Pneumocystis*,⁹ latent adenovirus,¹⁰ autoimmunity,¹¹ or repeated attempts at repair of airway damage.¹² Inflammation was present in the small airways of surgically resected lung specimens from individuals up to 9 years after smoking cessation,⁷ and in induced sputum, BAL fluid, and mucosal biopsies in COPD patients who were not currently smoking.¹³ Inflammatory changes following smoking cessation appear to be quite complex. A study of those with COPD who have successfully given up smoking compared with asymptomatic quitters revealed

persistent inflammation in bronchial biopsy specimens, while the number of sputum neutrophils and lymphocytes and the levels of interleukin-8 and eosinophilic cationic protein actually increased at 1 year. The duration of smoking cessation is also important because, with a longer duration, the CD8 cell numbers decrease, plasma cell numbers increase, while other inflammatory cells persist.¹⁴ Since oxidative stress (as reflected in protein carbonyl levels) also persists after smoking cessation, the relationship between oxidative stress, duration of cessation, and inflammatory markers needs further study.

There has been renewed interest in obstructive lung disease in the elderly. This population is at an increased risk of both pulmonary and systemic injury from tobacco smoke. The Health Aging and Body Composition study is a prospective cohort of individuals aged 70–79 years. In well functioning elderly subjects with or without obstructive lung disease, interleukin-6 is associated with reduced FEV₁, quadriceps strength, and exercise capacity.¹⁵ The findings of Nagai *et al* add the possibility that increasing oxidative stress with age may also contribute.

Perhaps the finding that oxidative stress increases with age is not too surprising. Older smokers are exposed to cigarette smoke over many years. Even in a healthy volunteer population, neutrophil counts in induced sputum increased with age,¹⁶ possibly as a result of exposure to pollutants. Smoking leads to age related decreases in antioxidant activity in alveolar

macrophages. There have been few attempts at targeting oxidative stress via supplementing antioxidants or boosting endogenous levels in the older smoker, but this certainly should be evaluated. As already mentioned, the benefits of smoking cessation can be seen regardless of age and include a decreased rate of decline in FEV₁, a lower risk of stroke or myocardial infarction, and meaningful life extension. Surprisingly, the elderly are less likely to receive smoking cessation advice than their younger counterparts.¹⁷ Clearly, as more research is performed on pathogenetic mechanisms such as oxidative stress in the elderly smoker, simultaneous attention must be paid to prevention.

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Post-infectious bronchiolitis obliterans in children

Insights into post-infectious bronchiolitis obliterans in children

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New information contributing to our understanding of risk factors predisposing to bronchiolitis obliterans in children

Bronchiolitis obliterans (BO) is a rare form of chronic obstructive lung disease that follows an insult to the lower respiratory tract.¹ It is characterised by inflammation and fibrosis of the terminal and respiratory bronchioles that lead to narrowing and/or complete obliteration of the airway lumen. Pathologically, two forms of BO

are recognised, and these may be part of a continuum. Proliferative bronchiolitis is characterised by intraluminal exudates, whereas constrictive bronchiolitis is characterised by alterations in the walls of the bronchioles ranging from inflammation to fibrosis and, ultimately, to complete obliteration of the lumen.² The histological findings of

constrictive bronchiolitis are a common end point for many disorders that are associated with airway epithelial injury including allograft recipients (lung, heart-lung, and bone marrow), previous lower respiratory tract infection (adenovirus,^{3–6} influenza,⁷ parainfluenza, measles, respiratory syncytial virus,⁸ or *Mycoplasma pneumoniae*^{9–11}), collagen vascular disease (especially rheumatoid arthritis and Sjogren's syndrome), toxic fume inhalation, chronic hypersensitivity pneumonitis, drugs (such as penicillamine or cocaine), and Stevens-Johnson syndrome.^{12–13} With the exception of specialised centres where large numbers of paediatric lung, heart-lung, or bone marrow transplants are performed, post-infectious BO is generally the most common form of BO in children worldwide.

For unclear reasons, post-infectious BO seems to occur more frequently in the southern hemisphere (Argentina,