



Mechanisms of chronic airway obstruction in smokers

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Summary Studies over the past few decades have showed a clear association between cigarette smoking and the development of chronic airway obstruction. Yet, only a minority of smokers is affected so that in many, even heavy, smokers, pulmonary function remains within normal limits. While carcinogens have been well characterized, there is only limited information about the constituents of cigarette smoke responsible for inducing chronic airway obstruction. In addition, the associated risks factors for airway obstruction in smokers have not been totally identified. The present paper is a review of the recently accumulated facts concerning the intimate action of cigarette smoke at the level of large and small airways and lung parenchyma. The role of classical inflammatory cells such as neutrophils and alveolar macrophages is reviewed, but emphasis is put on recent evidence indicating the involvement of CD8+ T-lymphocytes and possibly eosinophils in the genesis of the structural changes leading to airways obstruction. The mechanisms by which airway inflammation and remodelling cause airway narrowing and airflow limitation are discussed, along with the associated loss of lung elasticity secondary to destructive emphysema. Other biological, epidemiological, physiopathological, and clinical aspects are analyzed, stressing such fundamental aspects as the defence mechanisms, the morpho-functional correlations, the identification of susceptible smokers, and the early detection of airway obstruction, both in specialized laboratories and in primary care.

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Introduction

Evidence accumulated in the past 30 years shows an irrefutable association between the long-term inhalation of cigarette smoke and the development of obstructive airway disease.^{1–4} Cigarette smoke is

the most important factor associated with the occurrence of chronic airway obstruction, being responsible for 80–90% of cases of chronic airway obstruction in the USA.⁵ Deaths from chronic airway obstruction are several times more numerous and the loss of pulmonary function with age is more accelerated in smokers than non-smokers.⁶ In general, a dose–response relationship exists between the amount of tobacco smoked and the level of obstruction^{2,3} and a progressive reduction in mean flow rates and an increase in the incidence of severe obstruction with increasing pack-year

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exposure have been documented.⁴ However, in a significant number of heavy smokers, pulmonary function remains within normal limits, a finding indicating that other factors, either of genetic and/or environmental nature, are also involved in the production of airway obstruction.

Risk factors for the development of chronic airway obstruction

Several risk factors are likely to explain the susceptibility of smokers to develop airway obstruction and a thorough discussion on this topic is available elsewhere.⁷ Briefly, concerning cigarette smoke itself, the risk of airway obstruction does not seem to be influenced neither by the nicotine or tar content⁸ nor the addition of a filter.⁹ However, studies in adults have shown an increased prevalence of symptoms following passive smoke exposure at the workplace and at home¹⁰ while studies in children have demonstrated an increase in respiratory illnesses and a decrease in levels of pulmonary function especially when mothers smoke.¹¹

There is evidence that the rate of decline in forced expiratory volume in one second (FEV₁) in smokers is correlated with the subject's response to non-specific bronchial challenge. Studies in the general population have shown bronchial hyperresponsiveness (BHR) to be an important predictor of lung function^{12,13} while studies in large populations of subjects with early obstruction showed BHR to be a strong predictor of changes in FEV₁ (% predicted), after controlling for baseline lung function, age, sex, baseline smoking history and changes in smoking status.¹⁴

Another important factor likely to play a role in the development of chronic airway obstruction in response to smoking is genetic predisposition, the best illustration of which is the propensity to the development of early onset, familial emphysema in patients with α 1-antitrypsin deficiency.¹⁵ However, this enzyme deficiency is present in only 1–2% of obstructive patients and, although the homozygous deficiency state (Pi-Z phenotype) is clearly associated with the occurrence of emphysema, its presence may not suffice to produce airway obstruction. Indeed, in an earlier study we found that among six males with severe deficiency (homozygous Pi-Z phenotype) only four—all of whom were ex-smokers seeking help because of respiratory complaints—had severe functional impairment.¹⁶ The remaining two, who were first screened at a centre for preventive medicine, had

little or no symptoms and remarkably well preserved mechanical function despite active smoking and similar α 1-antitrypsin blood levels. As a whole, this highly deficient group was clinically and functionally indistinguishable from a non-deficient group of similar age and tobacco consumption.

Other risk factors which have been associated with the development of chronic airway obstruction include age, air pollution, childhood illnesses, occupation, social class, and alcohol use.¹⁷ However, the extent to which these factors act individually or in combination to increase the risk of airway obstruction is not completely known. More studies are necessary to clarify this important issue.

Cigarette smoke-associated syndromes

Smoking-induced lung diseases are complex and can be defined clinically (chronic bronchitis), pathologically (emphysema) and functionally (chronic airway obstruction).¹⁸ This triple description reflects differences in the way the various authors recognize and describe the cigarette smoke-related diseases. Therefore, it is important to realize that chronic airway obstruction is not one disease but a term encompassing at least three phenotypes namely obstructive chronic bronchitis, emphysema, and small airway disease. The diagnosis of obstructive chronic bronchitis is based on the objective documentation of airway obstruction and symptoms of cough and sputum production.¹⁸ Incidentally, smokers who consider themselves "healthy" may develop mild symptoms which are related to physiological changes and inflammatory markers reflecting events in the central rather than the peripheral airways.¹⁹ Emphysema is defined in anatomical terms as a permanent destructive enlargement of the airspaces distal to the terminal bronchioles.¹⁸ Finally, small airway disease is defined as a functional abnormality not revealed by standard spirographic tests such as the FEV₁,²⁰ evidenced by the use of so called "sensitive tests", and by peculiar anatomic alterations.

Understanding airflow limitation

To understand how tobacco smoke induces the development of airway obstruction it is useful to revise the mechanisms of airflow limitation. The tracheobronchial tree is a highly branched system of conducting tubes which can be divided schematically into large airways (airways with cartilage in

their walls, usually greater than 2 mm in internal diameter) and small airways or bronchioles (airways without cartilage in their walls, usually less than 2 mm in internal diameter). Distal to the bronchioles is the terminal bronchiole, and beyond it the acinus. The branching of the tracheobronchial tree would be symmetric if each parent branch divided into two daughter branches of equal diameter and length. In fact, the system is slightly asymmetric, with the diameter of two daughter branches being greater than the diameter of the parent branch and the number of airways increasing more than the diameter of the individual airways decreases.²¹ In such a system, the major site of airway resistance does not lie in the smallest airways as might be expected from rational considerations but in the medium sized bronchi, with most of the pressure drop occurring in the airways up to the seventh generation.²² The reason is the enormous increase in the cumulated cross-sectional area of the airways, from the trachea to the lung periphery, which explains the noticeable diminution of flow resistance in the peripheral airways. Although initial measurements suggested that less than 20% of airway resistance could be attributed to airways less than 2 mm i.d.,^{23,24} later experiments showed that 30–40% is probably a more realistic figure.²⁵

In a system like the tracheobronchial tree, airflow can be limited either by reducing the pressure applied to the system or by narrowing the tubes (bronchi), or both. The pressure applied to airflow is the recoil pressure of the lung, which is determined by its elastic properties. Airway narrowing is usually characterized by parameters of forced expiration, and the mechanisms of flow limitation during this manoeuvre can be explained on the basis of the simple model proposed by Mead and colleagues.²⁶ At end-inspiration, immediately before forced expiration, flow is zero and intrabronchial pressure, i.e. the pressure within the airways from the mouth to the alveoli, is atmospheric. At the same time, the pressure surrounding the airways (intrapleural) is negative and equal to the static recoil pressure of the lung. This interplay makes the pressure difference between the airway lumen and the intrapleural pressure to be positive thus tending to expand the airways (Fig. 1a). Early in forced expiration, both intrapleural and alveolar pressures rise greatly. As air flows, intrabronchial pressure drops to a point where it equals intrapleural pressure. Downstream from this "equal pressure point" (EPP) airway collapse occurs and flow is determined only by the difference between alveolar pressure and intrapleural pressure. Beyond the EPP the airway resistance is irrelevant. At high

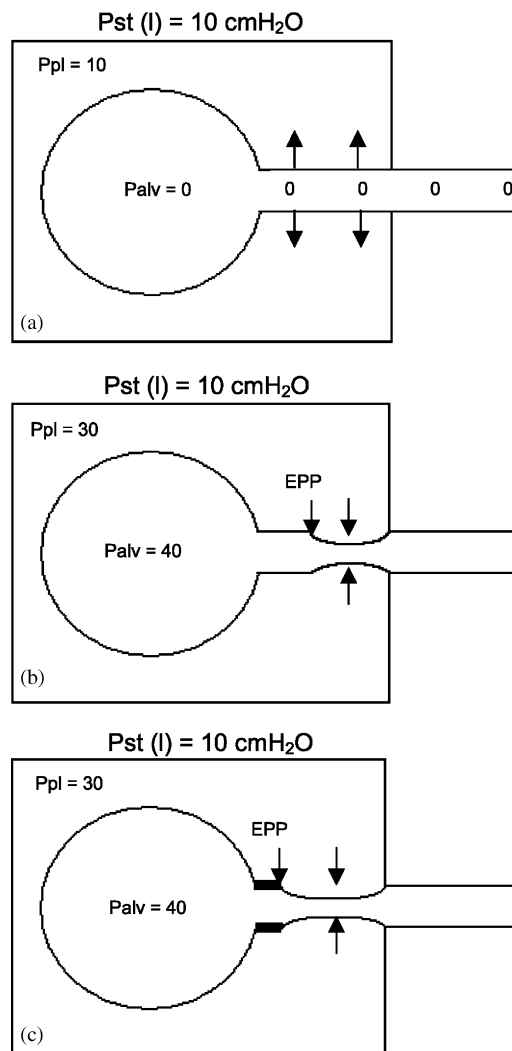


Figure 1 Model of lung to illustrate airflow limitation in healthy subjects and smokers with small airway disease (see text for discussion). (a) End-inspiration, normal. (b) Forced expiration, normal: EPP in lobar bronchi; dynamic compression. (c) Small airway disease: EPP moves toward periphery; dynamic compression.

lung volume (e.g. end maximal inspiration), the EPP is located in central airways, probably in the vicinity of lobar bronchi, where the cumulated cross-sectional area is small. As lung volume decreases, the EPP moves toward the periphery so that at low lung volumes flow is dependent of the resistance of the airways between the alveoli and the EPP, i.e. the small airways (Fig. 1b). In cigarette smokers, peripheral airway resistance can be increased by changes in the airways themselves (e.g. inflammation, swelling of the mucosa, contraction of smooth muscle, retention of secretions, etc.) or in the static (e.g. destruction of alveolar attachments, decrease in lung recoil) and dynamic (e.g. dynamic compression) forces acting upon them (Fig. 1c). Other factors favouring

this "dynamic narrowing" include the magnitude of the flow and the compressibility of the airways.

Factors involved in cigarette smoke-induced airway obstruction

Although cigarette smoking is the major cause of chronic airway obstruction only 24–47% of the smokers actually develop clinically significant airway obstruction.⁶ Among the environmental factors likely to influence an individual's response to cigarette smoke, the smoke composition and mode of delivery play an important role.

Smoke components involved in the pathogenesis of cigarette smoke-induced obstruction

Cigarette smoke is a complex, heterogeneous mixture of about 4000 substances. By convention, the smoke fraction that passes through a glass fibre filter is referred to as the *gas phase* and the retained fraction as *particulate phase*.⁵ Main gas phase components include carbon dioxide (CO₂), carbon monoxide (CO), irritants, and carcinogens. Particulate phase is a mixture of nicotine and tar, a generic term used to define the particles of smoke and the condensable components of the gas phase, minus nicotine and water. Tar contains various aromatic hydrocarbons, including carcinogens (e.g. non-volatile nitrosamines, aromatic amines, benzopyrene) and radioactive elements (e.g. Polonium-210). The composition of the smoke directly inhaled through the cigarette into the lung (*mainstream smoke*) is different from that formed between puffs (*sidestream smoke*) and that exhaled (*exhaled smoke*), both constituting the smoke breathed by passive smokers. Unlike carcinogens, which have been well characterized, there is only limited information about the constituents of cigarette smoke responsible for inducing chronic obstructive lung disease.

Several studies failed to demonstrate a clear, direct association between the *tar yield* and the development of airway obstruction. Higgenbottom and colleagues²⁷ related the tar yield and the number of cigarettes smoked daily with lung function and respiratory symptoms in more than 18,000 male civil-servants. They found that tar yield influenced phlegm production but *not* the degree of airflow obstruction, and suggested that the irritant agents leading to obstruction were probably contained in the *gaseous phase* of tobacco smoke. Paoletti and colleagues²⁸ examined 582

smokers and 621 ex-smokers and found that the estimated *tar* exposure from current cigarette consumption was significantly associated with cough and phlegm, *and* lung function measurements. Petitti and Friedman²⁹ examined the association between smoking cigarettes with low yield of tar and nicotine and respiratory diseases by reviewing the medical records of 4610 current smokers and 2035 never smokers. They found that smoking *lower tar* cigarettes was not associated with a lower risk for chronic obstructive pulmonary disease. Brown and colleagues³⁰ observed that for women but not for men, the rates of chronic cough and chronic phlegm were higher with higher tar yield of cigarettes smoked. However, pulmonary function tests were not done so the relationship between tar yield and the degree of airway obstruction could not be examined. Finally, Krzyzanowski and colleagues⁸ analyzed data collected in the Tucson Epidemiologic Study of Airway Obstructive Disease and found that the tar, nicotine, and CO contents were important only in connection with the *number* of cigarettes smoked and had no independent effect on pulmonary function.

There is no evidence of a direct relationship between the *nicotine yield* and the development of airway obstruction.^{8,31} However, nicotine was found to be chemotactic for human neutrophils,³² the first cell to be recruited in smoke-induced lung inflammation, and could therefore play an important role in the onset of the lung response eventually leading to airway obstruction (see below).

Several *irritant substances* (e.g. acrolein, cresol, acetone, phenol, etc.) present in the two phases of smoke can act either directly on the airways, damaging the mucocilliary apparatus of the bronchial mucosa and favouring the development and progression of bronchitis, or indirectly, favouring lung destruction. This is the case of the potent irritant acrolein, which appears to favour the release by alveolar macrophages of leukotriene B₄, a chemotactic substance responsible for the recruitment of neutrophils in the lung parenchyma, the presumed first event leading to emphysema.³³

Finally, the role of *free radicals*, which are present in both smoke phases, as agents favouring the development of emphysema and airway obstruction seems now well established.³³ In gas phase, free radicals react with oxygen to form oxy-radicals in smoke, and inactivate alpha-1-protease inhibitor (α 1PI) in a 2-step process: a fast reaction, which is completed in minutes, and a slower process which continues for hours or days. Free radicals in the particulate (tar) phase are stable indefinitely, and are capable of reducing molecular oxygen to produce superoxide,

eventually leading to hydrogen peroxide and hydroxyl radicals.

Smoking parameters in the development of airway obstruction

The manner of smoking is one of the major factors controlling lung's exposure to cigarette smoke. In general, smokers take a puff into the mouth and after a variable pause mix the smoke with air and inhale. The reason why this two-phase pattern is adopted is not clearly understood but it could be a means to reduce the acute airway response to smoke inhalation. Deposition of particles of smoke depends on their size, the pattern of breathing, and the pulmonary structure-function relationships. The median size of particulate matter in smoke ranges from 0.3 to 0.5 μm but it may increase in actual smoking, with growth in size occurring by coalescence or by hygroscopic growth after absorption of moisture in the respiratory tract. Larger particles tend to deposit in airway branch points by impaction, while smaller particles tend to deposit by sedimentation in areas of slowest flow, at the lung periphery.

Individual smokers show a wide variation in the volumes inhaled while smoking a single cigarette whatever the tar yield. Using respiratory inductive plethysmography, Tobin and colleagues³⁴ assessed the pattern of inhalation in 19 habitual smokers. They found that the mean volumes inhaled varied from 0.27 to 1.97 l (mean \pm SD = 0.79 \pm 0.45) and the mean duration of smoke inhalation varied from 2 to 6.8 s (mean \pm SD = 4.5 \pm 1.3). In addition, they found that the smokers' perception of their inhaled volume was quite imprecise and pointed out that such imprecision could be responsible for the purported lack of relationship between smoke inhalation and loss of lung function.³⁵ Another study from the same group showed that in a single session of 150 min, switching from a high- to low-tar cigarette caused a significant increase in the puff volume from 39 \pm 10 to 52 \pm 15 ml, respectively ($P < 0.001$).³⁶ It was argued that if the gas phase is the important component for the development of airway obstruction, subjects taking larger puff volumes may be at an increased risk of obstruction.

The inhalation pattern seems to be important in the pathogenesis of airway obstruction, and smokers with obstruction have patterns that differ from those of smokers without obstruction.³⁷ In addition, higher ventilation/perfusion ratios in the lung apices could lead to excess deposition of smoke in these areas thus explaining the preferential localization of centriacinar emphysema.³⁸ Longitudinal

studies comparing objective indices of smoke inhalation and pulmonary function are necessary to assess the importance of inhaling patterns in determining loss of lung function.

Pulmonary response to the inhalation of cigarette smoke

In healthy individuals, a complex system called "host defence mechanisms" limits the penetration of substances through the mucosal surface and removes particles deposited along the airways and in the alveoli. These mechanisms include anatomic barriers in the airways, clearance activity provided by coughing and the mucociliary apparatus, and several substances of non-immunologic and immunologic nature. The upper regions of the bronchial tree are lined with ciliated cells, the "mucociliary escalator", in charge of removing inhaled particles from the lungs. Chronic cigarette smoking may induce an increased number of abnormal cilia which could constitute a determinant of the mucociliary clearance impairment.³⁹ Airways beyond generation 14 do not have this protection, being therefore vulnerable to the effects of inhaled particles, especially those in the respirable range (0.5–5 μm) such as particulate matter of smoke (median size = 0.5 μm). Despite the efficiency of host defences, during cigarette smoking 5–10% of the tar/nicotine particles are deposited in the tracheobronchial region and 30–40% in the alveolar region. Obviously, the amount of deposited substances and the site of deposition may vary according to the physical properties of the smoke particles and the smoking pattern (volume and depth of inhalation, etc.). For the average smoker, particle deposition is greatest at airway bifurcations, the most common site of bronchogenic carcinoma. The chronic, continuing action of cigarette smoke on lung structures induce an array of lung responses that will eventually lead to airway obstruction in the susceptible smoker. The initial event after the first few cigarette puffs is an alteration of the airway epithelial cell barrier leading to airway inflammation. Several studies have shown that this inflammatory process is quite widespread and extends to the central airways,^{40,41} peripheral airways^{24,42–44} and lung parenchyma as well.^{45,46}

Airway inflammation

It has long been recognized that exposure to cigarette smoke is associated with airway

inflammation.⁴⁰ The combination of direct effects of cigarette smoke and indirect damage caused by effects of inflammatory cells leads to a series of epithelial changes including squamous metaplasia, hyperplasia of mucous glands, changes in mucociliary clearance, and fibrotic changes. Several types of inflammatory cells are thought to play a role in this process.

An increase of *neutrophils* in the airway lumen has been documented by bronchoalveolar (BAL) fluid and sputum analysis in smokers with mild to moderate chronic airway obstruction^{47–50} and a good correlation was observed between the number of neutrophils and the annual decline in FEV₁.⁴⁷ However, biopsies studies in mild to moderate airway obstruction showed a dissociation between the increased number of neutrophils in the airway lumen and a lack of increase in these cells numbers in the subepithelium.⁴¹ To explain this discrepancy, Saetta and her colleagues postulated that neutrophils could migrate across the tissue into the lumen thus making their accumulation undetectable by tissue analysis but detectable by analysis of BAL fluid or induced sputum.⁵¹ Incidentally, studies of surgical specimens and biopsies by the same team showed an increased number of neutrophils in both epithelium and bronchial gland of patients with established chronic airway obstruction thus providing evidence for neutrophilia not only in the airway lumen but also in specific areas in the airway wall of these subjects.⁵²

Another cell involved in the process of smoke-induced airway inflammation is the *T-lymphocyte*. Studies of bronchial biopsies taken through a bronchoscope or from surgical specimens have shown these cells to infiltrate the epithelium and submucosa of patients with mild to moderate airway obstruction, along with macrophages and eosinophils.^{41,52–57} Using immunohistochemical methods various studies showed that in contrast with asthma—whose inflammation is dominated by the CD4+ subset—in chronic airway obstruction the T-lymphocyte inflammation is largely due to the CD8+ subset thus making the balance of the CD4+/CD8+ cell ratio to tilt in favour of CD8+ cells. Concerning lung distribution, the CD8+ infiltrate was found to be ubiquitous, being present in all lung compartments including the central airways^{52,57–59} the peripheral airways^{59–61} and the lung parenchyma.⁶²

The role of T-lymphocytes in smoke-induced airway inflammation has been explored by several authors. In a study examining the effect of smoking on small airway submucosal immunopathology, Lams and colleagues⁶¹ found an increase in total and activated eosinophils, neutrophils, and CD8+/

CD3+ cell ratio in smokers along with a decrease in CD4(+)/CD8(+) cell ratio. Interestingly, the increased CD8+/CD3+ cell ratio showed a dose relationship to pack-years smoked and an inverse relationship to months since smoking cessation suggesting an association between cigarette smoking and CD8+ cells. In bronchial biopsies of bronchitic smokers with and without chronic airway obstruction O'Shaughnessy and colleagues⁵⁷ found that as airflow obstruction develops, neutrophils and CD8+ lymphocytes increase in number and proportion in association with the decline of lung function. These authors suggested that individuals with genetically determined higher CD8+ cell population may be more susceptible to a further increase in CD8+ cells recruitment induced by smoking and that this might explain why only a proportion of smokers proceed to develop chronic airway obstruction. Saetta and her colleagues⁶⁰ examined whether the inflammatory process in the small airways differs in surgical specimens of smokers with ($n = 9$) and without ($n = 7$) chronic airflow obstruction. They found that the number of CD8+ T-lymphocytes and the smooth muscle area were increased in smokers with obstruction, while the number of neutrophils, macrophages, and CD4+ lymphocytes were similar in the two groups. When all the smokers were considered jointly, both the number of CD8+ T-lymphocytes and the value of smooth muscle area showed a significant negative correlation with FEV₁. Taken together, these studies support the idea that the CD8+ cells might play a role in the development of smoke-induced airway obstruction.

In contrast with T-lymphocytes, the role of *eosinophils* in the pathogenesis of chronic airway obstruction in smokers is more controversial. While airway eosinophilia has been documented in smokers with chronic obstruction during exacerbations,⁵⁵ an increase in eosinophils in clinically stable patients has been documented by some investigators^{48,54,61,63,64} but not by others.⁶⁵ On the other hand, eosinophilia has been documented in BAL lavage fluid in a subset of asthma-like patients with chronic airway obstruction who respond to steroid and have increased responsiveness.⁶⁶

The role of eosinophils in the development of chronic airway obstruction in smokers is still controversial. Lams and colleagues⁶¹ used immunohistochemistry to examine peripheral lung sections obtained at surgery from smokers ($n = 22$), ex-smokers ($n = 17$) and non-smokers ($n = 5$). The number of eosinophils and activated eosinophils in the small-airway submucosa of smokers was increased compared with non-smokers. In addition, a good correlation was found between the number of

eosinophils and neutrophil numbers. However, no difference was found between groups with and without airway obstruction in the number of eosinophils infiltrating the submucosa, a finding suggesting that eosinophilia may be related to smoking per se. Balzano and colleagues⁵⁰ evaluated airway inflammation by cellular analysis and measurement of eosinophil cationic protein (ECP) levels in induced sputum and correlated the inflammation markers with functional indices of obstruction. A group of 46 subjects with clinically stable chronic obstructive pulmonary disease ($n = 10$), patients with mild asthma ($n = 15$), asymptomatic smokers ($n = 11$), and healthy control subjects ($n = 10$) was examined. As expected, eosinophils were found to be significantly higher in patients with asthma than in the other groups, while neutrophils were significantly higher in patients with chronic obstructive pulmonary disease than in the other groups. However, eosinophils and ECP levels were increased in patients with chronic airway obstruction as compared with healthy controls. In addition, sputum eosinophils and sputum ECP levels were inversely correlated with indices of obstruction both in patients with established chronic airway obstruction and asymptomatic smokers. Finally, significant correlations were found between sputum eosinophils and neutrophils as well as sputum neutrophils and sputum ECP, leading the authors to conclude that eosinophilic and neutrophilic inflammation may be closely correlated and that eosinophils may play a role in the pathogenesis of chronic airway inflammation in chronic airway obstruction.

To summarize, there is evidence that neutrophils, CD8+ cells, and possibly eosinophils play a role in cigarette smoke-induced chronic airway obstruction. While neutrophils predominate on mucosal surface of large airways, CD8+ cells are distributed extensively along all lung compartments. This is especially true of mild and moderate obstruction; as more severe airflow limitation develops the number of neutrophils increases suggesting that these cells may play a role in the progression of the disease. Finally, an increase in the number of eosinophils—which correlated with the neutrophil numbers—has been documented in the sputum and small airway submucosa of patients with stable chronic airway obstruction and smokers, respectively.

Inflammation in the lung parenchyma

As discussed above, smoking is known to be associated with the presence of neutrophils in the distal airspaces.⁶⁷ The exact mechanisms governing

neutrophil recruitment and sequestration are not completely understood but it seems that the process is influenced by a loss of capacity of neutrophils to deform, an important mechanism allowing these cells to squeeze through pulmonary capillaries, along with other factors.⁶⁸ This decreased deformability would delay the passage of neutrophils through the alveolar capillary bed thereby enhancing the release of elastase and reactive oxygen intermediates. These substances would then be capable to cause tissue destruction through the association of a protease–antiprotease imbalance and an oxidant–antioxidant imbalance. According to this theory, under normal circumstances proteolytic enzymes (e.g. elastase, cathepsin G) and matrix metalloproteases of neutrophil origin are neutralized by the antiprotease protective mechanisms (e.g. $\alpha 1$ AT); however, in smokers, this antiprotease activity is impaired by the oxidation of $\alpha 1$ antitrypsin by cigarette smoke. As a consequence, the unopposed proteolytic activity damages the lung parenchyma by degrading elastin, enhancing neutrophil recruitment, and increasing collagen deposition. Of course, neutrophils are not the only source of elastolytic enzymes and other cells, especially the alveolar macrophage, source of macrophage elastase, likely play a role. In fact, neutrophils and alveolar macrophages could interact but their relative contribution to the process of lung inflammation and emphysematous destruction is not completely understood.

Studies showed that the cellularity of the alveolar walls is increased in smokers. Eidelman and co-workers⁶⁹ examined the lungs of smokers ($n = 22$) undergoing thoracotomy for localized pulmonary lesions, along with lungs of eight non-smokers and five smokers who died suddenly of non-respiratory causes. The number of inflammatory cells correlated significantly with an index of alveolar destruction while the number of polymorphonuclear cells in smokers was 5 times as great as in non-smokers; however, the inflammatory cells were not clearly distinguished from one another. To attempt to clarify this issue, Saetta and colleagues⁶⁰ examined surgical specimens from non-smokers ($n = 8$), asymptomatic smokers with normal lung function ($n = 6$), and smokers with chronic airway obstruction ($n = 10$). Compared with non-smokers, smokers with airway obstruction were found to have an increased number of CD8+ cells both in the lung parenchyma and the pulmonary arteries. In addition, the number of CD8+ cells in both sites was significantly correlated with the degree of airflow obstruction. These results show that the lung parenchyma (and the pulmonary arteries) is (are) involved by an inflammatory

process whose characteristics are similar to those previously documented in the central and peripheral airways. Finally, Saetta and her colleagues⁷⁰ reported that the level of small airway inflammation in smokers correlates with the destruction of the alveolar wall attached to the airways (alveolar attachments). They suggested that by-products of inflammatory cells could weaken the alveolar tissue and facilitate its rupture at the point where attachments join with the outer airway wall and where mechanical stress is maximal. As a result, two types of emphysema were described.⁷¹ The first, centrilobular emphysema, is characterized by focal destruction restricted to respiratory bronchioles and the central portions of the acinus; it is commonly found in smokers and is usually more severe in the upper lung regions. The second, panacinar emphysema, involves the destruction of alveolar walls in a uniform manner and is found in smokers who develop emphysema early in life and in subjects with a deficiency of $\alpha 1$ antitrypsin.

Summary of cigarette smoke-induced inflammation

How do inflammatory cells work to promote airway damage? Although each cell can work on its own it is likely that they work in concert. The following sequence of events has been proposed as an attempt to combine their inflammatory action.⁷² In the beginning, the inflammatory reaction would involve the neutrophil followed by the alveolar macrophage in the epithelial surfaces of the lung. These cells would damage epithelial cells and the interstitial protein structures, which would be processed into peptides and recognized by T cells, initiating their activation and proliferation. Once activated, T cells could recruit other neutrophils and alveolar macrophages, as well as eosinophils, to the site of inflammation. Indeed, CD8+ cells are capable of switching to IL-5 production, a well described eosinophil chemoattractor and activation cytokine, and producing IL-8, a powerful chemoattractor for neutrophils. By this mechanism, CD8+ cells may play a central role in coordinating the influx of eosinophils and neutrophils in smoke-induced small airway inflammation.

Airway remodelling and lung destruction: the morphologic basis of airflow limitation

It has been known for 35 years that the increase in airways resistance in patients with chronic airway obstruction is due to disease in the peripheral airways.²⁴ Airway remodelling is the term coined to

define the structural changes that occur in the airway wall due to acute inflammatory events and/or chronic inflammation and repair. Several studies have shown that airway remodelling and inflammation in the small airways are associated with chronic airway obstruction.⁷³⁻⁷⁵ These processes combine with proteolytic lung destruction to decrease maximal expiratory flow from the lung.

When a bronchiole is cut in cross-sections three compartments can be distinguished: (1) *the inner wall*, that is the tissue between the luminal surface and the innermost layer of smooth muscle cells; (2) *the smooth muscle*, formed by discontinuous bundles arranged in a helicoidal fashion around the airway; and (3) *the adventitia*, a layer of loose connective tissue placed between the airway smooth muscle and parenchyma. In chronic airway obstruction, the airway remodelling affects these three layers. In the acute phase of chronic airway obstruction, there is an increase in deposition of submucosal and adventitial tissue due to oedema and proteoglycan deposition, two potentially reversible phenomena. With chronic inflammation, there is progressive collagen deposition and fibrosis of the airway wall together with smooth muscle remodelling due both to hypertrophy and hyperplasia. Mucosal thickening can amplify the effect of muscle shortening, adventitial thickening can lead to greater muscle shortening, and muscle thickening will lead to greater muscle shortening against elastic loads. As a result, in airway remodelling, a given degree of smooth muscle contraction will cause airway narrowing several fold greater than it would be observed in a non-remodelled airway.⁷⁶

Smoke-induced airway obstruction: morpho-functional correlations

There is evidence that the inflammatory changes in the small airways make an important contribution to the functional changes seen in smoke-induced chronic airway obstruction. Niewoehner and colleagues⁴² were the first to identify the pathological abnormalities in the small airways of young cigarette smokers. They compared the lungs of young smokers and non-smokers dying of sudden, non-hospital deaths and found that the former had a respiratory bronchiolitis associated with clusters of pigmented alveolar macrophages and an increase in mural inflammatory cells and denude epithelium in the membranous bronchioles; they postulated that these abnormalities were precursors of centriacinar emphysema. Cosio and colleagues⁷⁴ confirmed and extended these observations

by performing pulmonary function tests in 36 patients, of whom two were non-smokers, 1–3 days before open-lung biopsy for localized pulmonary lesions. Using an original pathologic score, they observed a progressive inflammatory reaction in the small airways leading to fibrosis with connective tissue deposition in the airway walls, the most severe cases showing a substantial degree of emphysema. They also observed that pulmonary function deteriorated progressively as the abnormality in the small airways increased, and that tests of small airway function were able to separate subjects with minimal pathologic changes from those with the most normal airways. These initial observations were largely confirmed by other investigators in experiments with lungs obtained either at surgery or autopsy.^{77–79} In conjunction, these studies demonstrate that cigarette smoke can elicit an early inflammatory reaction in the membranous and respiratory bronchioles that can be detected by tests of small airway function in subjects with normal FEV₁.

The progressive nature of cigarette smoke-induced lesions has been further demonstrated. Hale and her colleagues⁸⁰ examined pathologic changes in the small airways and lung parenchyma of lungs obtained from persons with a history of long-term cigarette use and an established clinical and physiologic diagnosis of chronic airflow obstruction, and compared the findings with those of older, never smokers and persons who had smoked but did not have severe disease. They found an orderly progression of the pathologic lesions in the three groups along with an increase in the number of airways <400 μm in diameter. In the group with established chronic airway obstruction, the pre-mortem FEV₁ correlated not only with the average airway diameter and the proportion of airways smaller than 400 μm, but also with emphysema. No small airway variable had any independent predictive value beyond the severity of emphysema alone in estimating the level of ventilatory function. However, as they pointed out, the relative importance of emphysema as a cause of severe airflow obstruction had to be tempered because correlations of individual spirometric function and pathology were possible only for the group of smokers with established COPD.

There is evidence that the pattern of airway obstruction differs according to the type of destructive emphysema.^{81–84} Panacinar emphysema is associated with a loss of elastic recoil and higher lung compliance whereas centriacinar emphysema is associated with a higher degree of airway inflammation and hyperresponsiveness. In pathological studies, lungs with centriacinar

emphysema were found to have higher total pathological scores of the small airways and more airways smaller than 400 μm than lungs with panlobular emphysema.⁸² As a consequence, in centriacinar emphysema, flow decreases as airways abnormalities increase, while elastic recoil loss would play an additive role. By contrast, in panlobular emphysema the flow limitation seems to be mainly a function of reduced elastic recoil. Saetta and her colleagues⁸⁴ showed that these two types of emphysema may be present in pure form or may overlap each other in which case, as they emphasized, one type is always clearly predominant. In these studies, pathological score for airway abnormalities were highest in pure centriacinar emphysema and decreased in stepwise fashion as the amount of panlobular emphysema increased. By contrast, lung compliance was highest in panlobular emphysema and decreased as the amount of centriacinar emphysema increased. Based upon these observations Saetta and her colleagues⁸⁴ suggested that panlobular emphysema might result from a bloodborne mechanism while centriacinar emphysema, which is characterized by an uneven pattern of lung destruction associated with more severe abnormalities in small airways, would be related to airborne factors. Finally, more recent studies have shown that high-resolution computer tomography (HRCT) may reveal early emphysematous lesions in a substantial fraction of smokers before clinical symptoms have developed.⁸⁵

An overview of the mechanisms likely to produce airway obstruction in the susceptible smoker is shown schematically in Fig. 2.

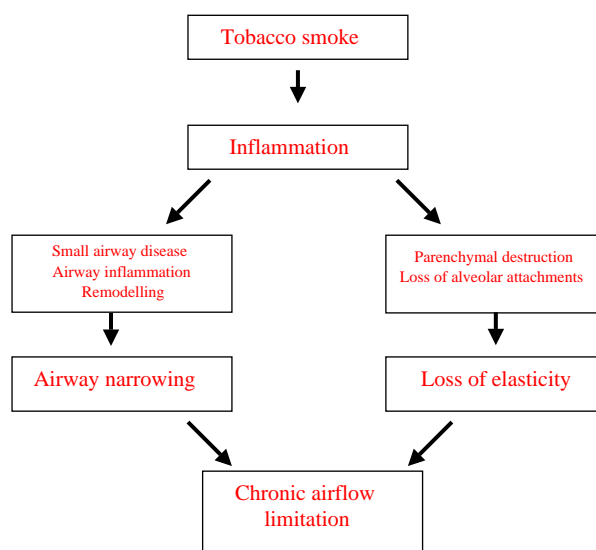


Figure 2 Schematic representation of the mechanism of cigarette smoke-induced chronic airway obstruction.

Cigarette smoke and airway obstruction: who is susceptible?

The risk for a smoker of progression toward chronic airway obstruction is linked to the rapid decline of FEV₁ with age. However, since FEV₁ is insensitive to early changes in the small airways, where the disease originates, other tests that correlate with lesions of the small airways should be available. In one study, Nemery and colleagues⁸⁶ indirectly estimated the prognostic significance of tests of small airway disease, namely the slope of phase III of the N2 single-breath washout and the bolus closing volume and closing capacity. They examined a group of steelworkers, 54 of whom were lifelong non-smokers and 105 current smokers, ranging between the ages of 45 and 55. Smokers were divided into 3 groups: the first group comprised the subjects with an FEV₁/FVC ratio below the normal limit value (66.6%) while the remaining subjects were divided into 2 groups according to the presence or not of an abnormal index of small airway function. The essential finding was that among smokers without evidence of airway obstruction the subjects with small airway disease had a significantly lower mean FEV₁ than smokers without small airway disease. The authors speculated that subjects with small airway disease and low normal FEV₁ might be at high risk of chronic airflow limitation.

The observations of Nemery and colleagues were further extended by Stanescu and colleagues.⁸⁷ In a 13 years follow up study of 56 subjects from the original series above, they showed that those subjects with impairment of tests of small airway obstruction but normal FEV₁/FVC ratio at the beginning of the study were at no obvious risk of rapid functional deterioration. However, in smokers with a decreased FEV₁/FVC, an associated high phase III slope quite accurately predicted a low FEV₁ at the end of the study. In their view, these smokers are probably the high-risk smokers who will reach clinical stages of COPD.

Early detection of obstruction in primary care

The decrease in lung function in patients with chronic obstructive lung disease is gradual and often diagnosed late in its course. In normal non-smoking subjects, FEV₁ declines on average approximately 30 ml per year.⁶ In susceptible smokers, the age-related decline in FEV₁ is accelerated and rates of decline from 60 ml/year⁸⁸ to 150 ml/

year⁶ have been reported. In a smoker having smoked for 30 years, such decline would cause the FEV₁ to decrease by 1.8–4.5 l, an amputation likely to cause disability or even death. Although smoking cessation does not usually allow FEV₁ recovery, it is the only effective treatment likely to reverse the steep decline in lung function at all stages of the disease.⁸⁸ By consequence, early detection of smokers at risk of development of obstruction is of utmost importance as a first step towards prevention. Indeed, smoking cessation can slow the rate of decline of FEV₁ both in subjects with mild airway obstruction⁸⁸ and with normal function.⁸⁹ In a study aimed at testing the efficiency of two regimens of nicotine replacement therapy for smoking cessation, we observed an average *increase* of 40 ml in the FEV₁ of completely abstinent subjects 1 year after smoking cessation.⁸⁹

The matter of how feasible is early detection in primary care has been addressed recently. In a random group of subjects visiting two semirural practices in the south east of the Netherlands, van Schayck and colleagues⁹⁰ found that 30 smokers, out of 169 (18%) capable to produce an acceptable spirometry, were at risk of chronic airway obstruction (defined as an FEV₁ < 80% predicted). Spirometry was carried out by a trained assistant in four minutes and the direct costs of detecting one smoker with airway obstruction was 5–10€. These and other results⁹¹ give support to the idea that smokers > 40–45 years of age who have a smoking history ≥ 10 pack years should be given a spirometric test especially if they are symptomatic.

Conclusion

In conclusion, a clear relationship has been documented between the chronic inhalation of cigarette smoke and the development of obstructive airway disease. A progressive reduction in mean flow rates and an increase in the incidence of severe obstruction have been found with increasing pack-year exposure. However, only a small fraction of smokers will develop significant airway obstruction, a finding suggesting that other genetic and/or environmental factors are also operative in the production of airway obstruction. Smoke components likely to cause airway obstruction are not completely known but nicotine, irritants such as acrolein and free radicals might play a role. The manner of smoking is another factor influencing the lung's exposure to cigarette smoke; a considerable inter- and intra-subject variability has been documented in the inhaled volume and puff volume.

After the first few cigarette puffs, an inflammatory response develops involving several cell types, especially neutrophils, alveolar macrophages, CD8+ T-lymphocytes, and possibly eosinophils. In susceptible subjects, a bronchiolitis develops which will progress with continuing smoking. After a variable time, airway inflammation is followed by airway remodelling, a term defining the structural changes that occur in the airway wall due to acute inflammatory events and/or chronic inflammation and repair. At the same time, the antiprotease activity of the lung may be compromised by the oxidation, by cigarette smoke, of antiprotease protective mechanisms (e.g. α 1 AT). Without opposition, the proteolytic activity may damage the lung parenchyma leading to destructive emphysema. This proteolytic lung destruction combines with airway inflammation and remodelling to produce decrease lung recoil and increased peripheral airway resistance, the two main factors responsible for decreasing maximal expiratory flow from the lung in cigarette smoke-induced chronic airway obstruction. Cigarette smoke-induced chronic airway obstruction is an insidious condition usually diagnosed at advanced stages. Since smoking cessation is the only treatment likely to reverse the decline in lung function an early diagnosis is a challenge of pulmonologists but also of general practitioners. The condition should be diagnosed as early as possible and subjects strongly advised to stop smoking.

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