THE PATHOGENESIS AND PATHOLOGY OF COPD: IDENTIFYING RISK FACTORS AND IMPROVING MORBIDITY AND MORTALITY*

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory condition of the lower airways that includes both emphysema and chronic bronchitis. COPD has some characteristics in common with asthma, but the distinction may be important because of different options for treatment. Development of COPD requires both exposure to noxious stimuli such as tobacco smoke as well as susceptibility to the disease, which is thought to be determined at least partly by genetics. The most important noxious stimulus, by far, is cigarette smoking; so many cases of COPD are preventable. Long-term studies of smokers show that COPD can be identified in its presymptomatic stages and that with smoking cessation, the rates of lung function decline and mortality can be reduced, even in the later stages of the disease. This means that progression to severe disease can be prevented in the vast majority of cases. For persons with more advanced disease, adherence to published guidelines for appropriate therapy can improve symptoms and quality of life, reduce exacerbations, and improve survival. These treatments include smoking cessation, and appropriate use of corticosteroids, long-acting bronchodilators, oxygen, and surgical interventions. Previous nihilistic attitudes about the treatment of COPD are no longer appropriate.


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The development of chronic obstructive pulmonary disease (COPD) requires both exposure to noxious agents and predisposition to the disease. The primary risk factor for COPD is tobacco use (predominantly cigarette smoking), however other environmental exposures may contribute, such as those found in certain occupations or living conditions. Of a group of people with identical exposure histories, whether to smoking or to other exposures, only a minority will develop COPD, and those who do will vary in the severity and manifestations of the disease. These discrepancies are thought to be due in part to genetic predisposition to COPD.

COPD RISK FACTORS

There are 2 types of risk factors for COPD: host factors (ie, inherent in the patient) and exposure to noxious stimuli (see Sidebar, page S745). Although intensity and duration of cigarette smoke exposure is an important determinant of the development of COPD, there is significant variability in COPD prevalence among smokers, illustrating the role that genetic predisposition plays. The most well-studied genetic disorder causing COPD is alpha-1-antitrypsin deficiency. Alpha-1-antitrypsin is a circulatory serine protease inhibitor. The body normally maintains a balance between serine proteases and their inhibitors, which are important in lung function. Alpha-1-antitrypsin deficiency is an autosomal recessive trait that occurs in roughly 1 of every 1000 persons of Northern European ancestry. Homozygotes for this trait experience accelerated decline in lung function and emphysema in both smokers and nonsmokers, although smoking greatly increases the risk and severity of COPD. Other host factors that contribute to the risk of developing COPD include asthma and airway hyperresponsiveness, although the mechanisms are not

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clear. Childhood respiratory illness and reduced lung growth (during gestation, due to low birth weight or childhood exposures) may also be markers for increased risk of COPD.1

Although many host factors cannot be modified, exposures to noxious stimuli are controllable and reversible contributing factors for the development of COPD. By far, the most common exposure linked to COPD is cigarette smoke, although other types of tobacco use, such as cigars and pipes, also produce increased morbidity and mortality from COPD. The increased risk for COPD with tobacco use is proportional to the magnitude of tobacco smoke exposure (eg, age at initiation of smoking, total pack-years smoked, and current smoking status). Not all smokers develop COPD, illustrating the role that predisposition (presumably mostly due to genetics) plays in the development of COPD.1 Exposure to occupational dusts and chemicals are not as common, and are present in more specific populations, based on type of employment (eg, grain handlers, coal miners). Exposure to irritants or sensitizing agents may create airway hyperresponsiveness that is additive with damage due to smoking or asthma.1 Similarly, exposure to indoor and outdoor pollution is confined to specific regions. Outdoor pollution has decreased appreciably in most cities in developed countries, and the exact components of outdoor pollution that trigger COPD are not known. Poor indoor air quality is produced not only by environmental tobacco smoke, or “secondhand smoke,” but also by use of “biomass” fuels and cooking oils without proper ventilation. Lastly, childhood viral infections may be more common in those who develop airway hyperresponsiveness, and thus an association is established between childhood infections and later development of COPD.1

COPD PATHOGENESIS

The lower airways begin at the terminal bronchiole and extend through the respiratory bronchioles and alveolar ducts to the alveoli. Lungs are perfused with blood via the pulmonary and bronchial arteries, through the pulmonary capillaries in the alveolar walls, leaving the lungs via the pulmonary veins. In COPD, inflammation causes direct destruction of lung tissues and also impairs defense mechanisms used to repair damaged tissues. This results in not only destruction of the lung parenchyma (ie, emphysema),

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**Table. Characteristics of Inflammation in COPD and Asthma**

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
</tr>
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<tbody>
<tr>
<td><strong>Cells</strong></td>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
<tr>
<td></td>
<td>Large increase in macrophages</td>
<td>Small increase in macrophages</td>
</tr>
<tr>
<td></td>
<td>Increase in CD8+ T cells</td>
<td>Increase in CD4+ Th2 cells</td>
</tr>
<tr>
<td><strong>Mediators</strong></td>
<td>LTB4</td>
<td>LTD4</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>IL-4, IL-5</td>
</tr>
<tr>
<td></td>
<td>TNF-alpha</td>
<td>Many others</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>Squamous metaplasia of epithelium</td>
<td>Fragile epithelium</td>
</tr>
<tr>
<td></td>
<td>Parenchymal destruction</td>
<td>Thickening of basement membranes</td>
</tr>
<tr>
<td></td>
<td>Mucus metaplasia</td>
<td>Mucus metaplasia</td>
</tr>
<tr>
<td></td>
<td>Glandular enlargement</td>
<td>Glandular enlargement</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td>Glucocorticosteroids have little or no effect</td>
<td>Glucocorticosteroids inhibit inflammation effectively</td>
</tr>
</tbody>
</table>

but also mucus hypersecretion, and airway narrowing and fibrosis.

A wide range of inflammatory cells and mediators are involved in the pathogenesis of COPD, namely neutrophils, macrophages, and CD8+ T cells in different areas of the lung. Although asthma and COPD share some inflammatory components, important differences distinguish the 2 diseases; however, they often coexist in the same patient. The characteristics of inflammation in COPD and asthma are compared and summarized in the Table. It is important to distinguish the 2 diseases during diagnosis because COPD appears to be poorly responsive to glucocorticosteroids as monotherapy, which are the mainstay of asthma treatment.

Overall, COPD pathogenesis can be summarized as resulting from a combination of genetic susceptibility combined with exposure to one or more risk factors, which leads to inflammatory processes that disrupt the balance of proteases and antiproteases (Figure 1). These abnormal inflammatory mechanisms result in tissue destruction, airway inflammation and remodeling, and ultimately airflow limitation (Figure 2). Of note, these imbalances and the presence of inflammation may result in a “positive feedback loop,” in which inflammation induces these imbalances, and the imbalances promote more inflammation.

Once the inflammatory responses are set in motion, 3 types of damage to the lung occur: disruption of the alveolar walls (or attachments), mucus hypersecretion contributing to airway obstruction, and fibrosis of the bronchioles (Figure 3). The pulmonary vasculature is also affected by inflammatory processes in COPD, which result in loss of capillary bed, lumenal narrowing, and ultimately increased pulmonary vascular pressure that appears first with exercise and then at rest as the disease progresses. Bronchiolitis results from repeated cycles of injury and repair to the bronchioles during exposure to noxious stimuli. Disrupted repair systems can lead to tissue remodeling affecting structure and function as well as scar tissue formation. The bronchioles, as part of the peripheral airways system, are the major site of airway obstruction in COPD.

COPD Presentation

During normal respiration, when air is taken into the lungs, the elastic alveolar walls and lung parenchyma are stretched and thus produce the pres-
sure necessary to expel the air during expiration. When the alveolar walls are damaged, recoil pressure is reduced. This not only reduces driving pressure for expiration, but also allows collapse of airways; thus, air in the lungs cannot be expelled fully, leaving an extra reservoir of air remaining in the lungs. Reduced elastic recoil can be demonstrated by the difference between blowing air into a balloon (normal alveoli) and blowing air into a plastic grocery bag (COPD). Persons with such lung damage and increased residual volume often present as the stereotypical COPD patient known as the “pink puffer.” They often have a barrel-shaped chest due to permanently overexpanded lungs. These patients often exhibit purse-lipped breathing and are not cyanotic or hypercapnic.

Airway lumenal obstruction occurs both because of the loss of elastic recoil, which holds the airways open, plus blockage of the airway lumen by mucus hypersecretions, mucosal thickening, and airway distortion. This increased airway resistance increases the work of breathing and contributes to labored breathing in virtually all patients with COPD. Lumenal obstruction can be illustrated by the difference between blowing air through a drinking straw compared with a cardboard tube from a roll of paper towels.

Persons with COPD can be hypoxemic for a number of reasons. In response to the increased work of breathing, some patients simply hypoventilate, become hypercapnic, and have a lower arterial oxygen content as a result. Others have normal, or even increased minute ventilation, but they have increased physiological dead-space, which reduces the efficiency of ventilation. Many have impaired gas exchange, which results in reduced oxygen uptake despite adequate ventilation and CO₂ elimination.

In some persons with advanced COPD with hypoxemia, the combination of hypoxic vasoconstriction plus loss of pulmonary capillary bed due to emphysema gradually leads to permanently increased pulmonary vascular resistance. Pulmonary hypertension is associated with the development of cor pulmonale (hypertrophy and dilation of the right ventricle) and is associated with a poor prognosis. Some COPD patients with severe hypoxia and pulmonary hypertension present another stereotypical picture, the “blue bloater.” These patients are typically hypoxic, hypercapnic, overweight, edema-

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**Figure 3. COPD Pathology**

In the peripheral airways of patients with COPD, there is airflow limitation due to loss of alveolar attachments, as well as inflammation, fibrosis, and mucus secretion, which result in obstruction of the airway. The contributions to airflow limitation from these processes vary from individual to individual. COPD = chronic obstructive pulmonary disease.


**Figure 4. Normal Lung Function Decline and the Impact of Smoking**

Fletcher and Peto showed that stopping smoking at any point during a patient’s life, even in the later years, can have important benefit in prolonging the onset of disability (in those who stop early enough in life) and death.

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second.

tous, and cyanotic, with a productive cough. The “pink puffer” and the “blue bloater” are stereotypes. Some patients present as one type or the other, but many COPD patients exhibit signs of both stereotypes.

Most patients with COPD develop chronic cough and sputum production even before they develop airway obstruction. However, dyspnea during exertion is the first symptom to herald the development of airway obstruction in COPD. The mechanisms leading to development of dyspnea are numerous and include combinations of the following: increased work of breathing, dynamic hyperinflation, decreased maximal ventilation, abnormal gas exchange, pulmonary hypertension and ventricular dysfunction, and peripheral muscle deconditioning (due to decreased use and oxygenation). The systemic effects of these mechanisms include nutritional deficiency and weight loss, and peripheral muscle weakness and loss of muscle mass. Along with the pulmonary and cardiovascular processes previously described, these lead to a progressive downward spiral of disease, dyspnea, deconditioning, disability, and ultimately death.

COPD IS TREATABLE

In the past, many healthcare practitioners have approached COPD with a nihilistic attitude, considering it incurable, untreatable, and self-inflicted. This attitude overlooks the fact that the vast majority of persons with COPD have mild disease, and that smoking cessation is benefited by aggressive coordinated support from medical caregivers. With early detection and intervention, these persons can prevent the development of severe disease. Furthermore, for the patients with advanced stages of disease, many interventions developed in recent years reduce the rate of decline in disease or reduce exacerbation frequency, improve lung function, quality of life, and improve survival. The magnitude of the effect of these interventions is the same or greater than much better publicized interventions for cardiovascular disease. The nihilistic attitudes of the past are thus obsolete.

The importance of early detection and intervention is worth stressing. Millions of persons have mild disease, and need not progress to severe disease. The impact of smoking on lung function has long been known, in part due to the seminal study by Fletcher.

**Figure 5. Impact of Smoking Cessation on Lung Function After 11 Years of Follow-Up: Results from the Lung Health Study**

Loss of lung function over the years of study among sustained quitters, continuing smokers, and intermittent smokers. Average values of postbronchodilator FEV₁ are shown, expressed in absolute measures (A), and as a percentage of the predicted normal value (B). COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second. Reproduced with permission from Anthonisen et al. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;166(5):675-679.

**Figure 6. Impact of Smoking on Clinical Presentation of Lung Function Loss**

People with COPD often lose 50% of their baseline function before they complain of symptoms (i.e., dyspnea, wheezing). COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second. Adapted with permission from Fletcher et al. The natural history of chronic airflow obstruction. BMJ. 1977;1(6077):1645-1648.
and Peto comparing the rate of decline in lung function among smokers versus nonsmokers. As shown in Figure 4, stopping smoking at any point in life, even in the later years, can have important benefit in preventing or delaying the onset of impairment and death. The results of the studies by Fletcher and Peto were confirmed by the Lung Health Study, a randomized clinical trial of smoking cessation in nearly 6000 middle-aged smokers with mild-to-moderate COPD. Analysis of lung function after 11 years confirmed that smoking cessation improves lung function and reduces mortality (Figure 5).

It is also important for healthcare practitioners to recognize that people who have supranormal initial lung function may lose as much as 40% of their initial lung function before they fall below “normal” values. People with COPD often lose 50% of their baseline function before they complain of symptoms (eg, prolonged respiratory infections, dyspnea, wheezing), as demonstrated in Figure 6. So, screening people who are at risk for COPD is critical to detect and stop the disease before severe damage develops.

For persons with more advanced disease needing symptomatic therapy, there is still cause for optimism, based on better-targeted and more effective therapy. Fibrosis and narrowing of the airways as well as disruption of alveolar walls and loss of elastic recoil are irreversible processes; however, other manifestations of COPD are reversible and respond to treatment. These include the accumulation of inflammatory cells in the peripheral airways, mucus hypersecretion, and smooth muscle contraction in the airways. Treatment of these reversible processes (see Managing COPD: Incorporating Guidelines into Primary Care Practice” by Dr Barry J. Make) offers improved longevity and quality of life for the COPD patient. In addition, recognition of the intermittent nature of COPD, with periods of relative stability punctuated by exacerbations, has led to a new style of therapy directed at preventing and treating exacerbations aggressively and proactively.

**CONCLUSION**

The most common noxious stimulus of COPD, by far, is cigarette smoking. However, not all smokers develop COPD, and COPD can develop in nonsmokers. Nonetheless, COPD is both preventable and treatable. Important studies of long-term smokers show that the rate of lung function decline and mortality can be positively affected by smoking cessation, even in the later stages of the disease. Our understanding of COPD pathogenesis shows that numerous aspects of this disease are not only preventable by cessation of smoking or other noxious exposure, but also are partly reversible in the later stages of the disease. Thus, COPD is a preventable and treatable disease. Obsolete nihilistic attitudes about therapy may result in missed treatment opportunities and are no longer appropriate for the majority of patients with COPD.

**REFERENCES**