The pathogenesis of chronic obstructive pulmonary disease

Abstract

Chronic obstructive pulmonary disease (COPD) is a slowly progressive condition characterized by airflow limitation, which is largely irreversible. Cigarette smoking is the main etiologic factor in this condition, far outweighing any other risk factors. The pathogenesis of COPD therefore is strongly linked to the effects of cigarette smoke on the lungs. The extent of smoking history and the severity of airflow limitation are generally related, but with huge individual variation. The pathogenesis of COPD encompasses a number of injurious processes, including an abnormal inflammatory response in the lungs to inhaled particles and gases. Other processes, such as failure to resolve inflammation, abnormal cell repair, apoptosis, abnormal cellular maintenance programs, extracellular matrix destruction (protease/antiprotease imbalance), and oxidative stress (oxidant/antioxidant imbalance) have also a role. The subsequent chronic inflammatory responses lead to mucus hypersecretion, airway remodeling, and alveolar destruction. This article provides an update on the cellular and molecular mechanisms of these processes in the pathogenesis. COPD is an inflammatory disease with active participation of macrophages, neutrophils, and CD8 lymphocytes, associated to oxidant stimulus which directly injures lung structure. These biochemistry reactions progressively develop alterations in small airways and take a new model of non-reversible pulmonary structural. Substances liberated by recruited cells and by oxidants stress brought temporary imbalance of pulmonary defense mechanism. This long time imbalance is one of the tools to up to date pathophysiology. The authors describe the relationship among structure, cells and biochemistry in COPD and its patho-physiological consequences.

Keywords: Pulmonary disease, chronic obstructive; Etiology; Inflammation.
Historic of COPD

A French physician, René Laennec, was the pioneer to describe pulmonary emphysema from observations of postmortem human lungs. He postulated that emphysematous lesions resulted from overinflation of the lung, which compressed capillaries leading to atrophy of the lung tissue. Until the end of the 1950s, this was the main theory of pulmonary hyperinflation.

These concepts were again reviewed at the Ciba Guest Symposium in 1959, which defined emphysema as “a distal expansion, abnormal and permanent, from the terminal bronchiole.” About 3 decades later, in 1985, a new Commission broadened the Ciba definition of emphysema by adding “destruction of the alveolar wall without obvious evidence of fibrosis.” Moreover, since chronic bronchitis and emphysema had airway obstruction as a common feature, these 2 entities were integrated into a single term, namely, chronic obstructive pulmonary disease (COPD). Normalization of lung function in respiratory function tests, either spontaneous or after the use of bronchodilators, was defined as bronchial reversibility and became one of the key points in the differential diagnosis of COPD and asthma.

In 1998, an international team of experts formed the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and prepared a consensus report to guide the global strategy on the diagnosis, management, and prevention of COPD. COPD was defined as a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.” Thus, the document completely redefined the concept of COPD. Inflammation was proposed as the main triggering factor and component of COPD; the terms “emphysema” and “chronic bronchitis” were no longer included in the definition; and cigarette smoking was suggested as the main risk factor for the disease. The devaluation of the importance of chronic bronchitis and emphysema, despite differences in clinical, therapeutic, and prognostic behavior, facilitated the understanding of COPD and its pathogenesis.

The rate of diagnosis of COPD in smokers is still low and reaches about 15%. This is owing to low sensitivity of spirometry in the early diagnosis. An increase in the residual volume and changes in chest computed tomography scans have not as yet been incorporated into the diagnostic criteria for COPD.

Today, COPD has the status of an epidemic. Our knowledge about inflammatory mechanisms involved in COPD and the current methods of diagnosing the early stage have not changed for decades, while it is estimated that the prevalence of COPD will continue to rise in the coming years.

Inflammation in COPD

The first findings on inflammation in centriacinar emphysema were reported in 1956 by Mc Lean and in 1957 by Leopold and Goug. At that time, the relationship between inflammation and emphysema was not generally acknowledged. In both studies, the samples were obtained during autopsy and could have been contaminated with bacteria after the death of patients and mimicked the patterns of “bronchopneumonia distal.” Linked to that was the idea on the pathological mechanisms and inflammatory responses, namely, that the pathogenic processes could heal without scarring or with scarring (fibrosis) and mild persistent inflammation, with heterogeneous and variable intensity.

During infection or smoke exposure, a large number of leukocytes and macrophages migrate to the lung where they are activated and start an inflammatory reaction, which, over the years, affects lung structure and function. The inflammatory process, which is usually unnoticed and continues over a prolonged period, occurs in the small airways (smaller than 2 mm
in diameter). It has been postulated that persistent inflammation in the distal respiratory tract of patients with COPD is responsible for the damage to bronchial epithelial cells. Thus, the alveoli and alveolar ducts coalesce irregularly and irreversibly.8

Inflammatory cells recruited to the lungs in COPD release substances such as elastase, collagenases, and oxidase products, which when superimposed by the oxidants inhaled from a cigarette smoke, change the proportional components of the extracellular matrix. Thus, an irreversible process is initiated, whereby the lung acquires a new, distorted structure (characterized by stretching and disappearance of cellular bulkheads, forming larger air spaces and compressions associated with the areas of hyperinflation in the bronchioles).9

Pathogenesis of COPD

The inflammatory mechanism of COPD involves various cells, interleukins, and oxidase products that together form an inflammatory mixture, which destroys the extracellular matrix, modifies lung structure, enhances the bronchial muscle, and fractures elastic fibers.

Elastic fibers were studied by several pathologists until the 1970s. Based on their findings, the lung has been described as an “elastic organ,” and this concept formed the basis of our pathophysiological knowledge about this organ10.

The involvement of the respiratory muscles in the pathogenesis of COPD has not been fully acknowledged. If atrophy, hypoplasia, hypertrophy, hyperplasia, or dysfunctional are doubts that require further investigation.10

Histopathological studies using immunohistochemical methods showed that lymphocyte CD8+ levels were significantly higher in patients with COPD than in control subjects. Findings on the involvement of CD8+ lymphocytes in COPD have been the major recent advancement in our understanding of the pathogenesis of this disease.11 (figure 2)

However, since it is unethical to perform serial biopsies in the same patient, other scienti-

Figure 1: Neutrophils in induced sputum of a patient with COPD.
tic methods for the structural analysis of COPD have to be developed to pursue these most recent advancements in pathophysiological knowledge.

Induced sputum was initially used as a method for microbiological diagnosis. In the 1990s, it was further developed and accepted as a research tool in asthma. In COPD, which is an inflammatory disease of the lower respiratory tract, induced sputum is still used to investigate the pathogenesis of the disease.\(^{12,13}\)

There is still little evidence in the literature on the changes in elastic fibers and bronchial muscles as well as the involvement of CD8+ T lymphocytes in the pathophysiology of COPD.

### Pathogenic theories of COPD

#### The Dutch hypothesis

Nonspecific bronchial hyperreactivity (HRB) is a state characterized by reduction in bronchial diameter triggered by inhaled stimuli. It is one of the pathophysiological mechanisms of a decrease in respiratory airflow in some obstructive diseases, especially asthma.\(^{14}\) In 1961, Orie et al.\(^{15}\) showed that HRB correlated with a decrease in the forced expiratory volume in 1 second in smokers. It was also reported in a subgroup of patients with COPD and was proposed as its possible risk factor. This theory became known as the Dutch hypothesis.\(^{16}\)

Studies on smokers and patients with COPD and asthma by using a bronchial challenge test with methacholine or histamine have shown that the level of HRB in some smokers was similar to that in asthmatic patients. Another finding was that HRB in smokers decreased after smoking cessation. Soon, cigarette smoke was considered as a factor causing bronchoconstriction.\(^{17}\)

In 1996, Taskin et al.\(^{17}\) showed that HRB was present both in patients with chronic bronchitis and emphysema, and that there were no statistical differences in the intensity and frequency of HRB between the groups.

HRB is one of the mechanisms of obstruction in COPD. The final comments that in the blood of nonasthmatic smokers may have increased certain occupational allergens, as well as, owning IgE and eosinophil values than in non-smokers and people with no allergic

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**Figure 2:** Measurement of CD8+ cells by an immunohistochemical technique in a patient with COPD.

Obs. Histological field – ×400. Patient with COPD and myeloperoxidase positivity in CD8+ cells (black arrows). Note their tendency to stay together. Atrophy of the septal area (green arrow) with the cells occupying the entire septum.
history, contributed to the revitalization of the Dutch hypothesis.18

Protease–Antiprotease Theory

Proteolytic enzymes are found in the granules of neutrophils and alveolar macrophages. Their function includes protecting the lungs through digestion of microorganisms, cellular debris, and coagulation products. Their proteolytic activity affects also the structural proteins of the lung.

Under certain conditions, such as infection or smoke exposure, large numbers of neutrophils migrate to the lung. Neutrophil enzymes are released in large numbers and in a haphazard way to protect the lungs. They recognize interaction sites but do not have the ability to distinguish between foreign and native proteins, so they may destroy both.

Neutrophil elastase is the main enzyme that degrades elastin, the structural component of elastic fibers. Under normal conditions, proteolysis is prevented by antiproteases, which are found in the blood, tissues, and bronchial secretions. Central to the pathogenesis of COPD is a protein inhibitor known as α1-antitrypsin.

In 1963, Laurell and Erickson19 linked the deficiency of α1-antitrypsin with emphysema. Significant lesions in lung structure have been shown to be caused by an imbalance between proteases and antiproteases. Based on this theory, some experimental models of COPD have been developed. However, the protease–antiprotease imbalance does not explain the pathogenesis of COPD in all affected patients. In fact, α1-antitrypsin deficiency is observed only in less than 1% of this patient population. It is associated mainly with one particular type of emphysema known as panacinar emphysema.

Oxidant–Antioxidant Theory

Cigarette smoke produced by tobacco combustion, which may be complete at the burning end of a cigarette, reaches the temperature of up to 850°C. The products of this oxidation undergo the following processes: pyrolysis (thermal decomposition with the formation of small organic molecules), pyrosynthesis (new substances derived from the recombination of fraction molecules), and distillation of some of the tobacco components (e.g., nicotine). The combination of these 3 mechanisms leads to the formation of a heterogeneous aerosol that contains both gaseous and particulate material (PM) (condensed organic compounds). Each compound in the smoke will partition between the gas and PM phases.

Cigarette smoke contains more than 4000 substances. The number and concentration of these substances depend on the climate and other region-related factors such as the methods of tobacco farming, preparation, and fermentation. The most-widely studied solid particles in cigarette smoke include nicotine, phenols, cresols, polycyclic aromatic hydrocarbons, organic acids, ketones, alcohols, and polyols. During the gas phase, the following substances are produced: nitrogen, oxygen, carbon dioxide, carbon monoxide, hydrogen, argon, methane, nonsaturated and saturated hydrocarbons, carbonyl groups, hydrocyanic acid, water vapor, nitrogen oxide, nitrogen dioxide, ammonia, formaldehyde, acetaldehyde, acrolein, propyl aldehyde, isovaleraldehyde, methyl acetone, butanone, furfuraldehyde, dimethyl and methyl furanacetic acid, acetonitrile, benzene, toluene, xylene, methyl chloride, derived carbonyl groups, and various organic acids.

The respiratory tract is constantly exposed to the effects of oxidation. The molecules of oxygen, ozone, nitrogen dioxide, sulphur dioxide, and cigarette smoke have a strong oxidative effect. During respiratory infections, oxidants can also be formed by granulocytes and macrophages. These cells use oxidation products to destroy microorganisms that enter the body through the respiratory system. However, during this process, oxidative activity also causes injury to the surrounding tissues. To prevent this effect, the respiratory tract uses various substances, such as vitamin C, glutathione, uric acid, bilirubin, vitamin E, vitamin
A, and albumin, which can block the action of oxidative molecules.

The oxidizing agents may increase the amount of mucus secreted by the bronchial glands, increase the migration of neutrophils to the lung, inactivate antiproteases, and inhibit fibroblast proliferation.20

Alterations in the balance between oxidants and antioxidants have been reported in various lung diseases, including acute respiratory distress syndrome, asthma, idiopathic pulmonary fibrosis, and COPD. The imbalance in the lungs is mainly caused by prompt and direct exposure to oxidative substances contained in cigarette smoke and polluted air, which leads to oxidative stress.

Imbalance of lymphocyte subsets (CD4 and CD8)

In 1995, Amadori et al.21 reported that 5% of healthy blood donors had the CD4/CD8 ratio lower than 1. Considering that COPD develops only in about 15% of smokers, they suggested that the lowest CD4/CD8 ratio could identify a group of patients with higher susceptibility to COPD. This continues to be one of the possible explanations of the pathogenesis of COPD.

Theory of latent viral infection

In 1997, Keicho et al.22 suggested the involvement of viruses in the pathogenesis of COPD. They observed the presence of adenoviruses in the epithelial cells of the lower respiratory tract in patients with stable COPD. Thus, they hypothesized that latent viral infection could be another factor (in addition to smoking and infection) triggering inflammation in patients with COPD, releasing inflammatory mediators, such as intercellular adhesion molecule 1 and interleukin 8, and intensifying the inflammatory process already initiated by smoking. Other advocates of viral involvement in the development and exacerbation of COPD have reported also the presence of respiratory syncytial virus in some patients. Thus, it can be assumed that latent viral infection in patients with COPD may affect direction intensity of inflammation in the lower respiratory tract.

Inflammatory/Immune Theory

In the 1990s, several groups of experts investigating the pathogenesis of COPD began to link the theories about the protease–antiprotease and oxidant–antioxidant imbalance and view them as representing a single pathogenic process. The findings related to both theories were interpreted together and an inflammatory model of COPD was proposed, with the major focus on the activity of macrophages and neutrophils.23

Other studies conducted during the same decade examined lung biopsy specimens and showed that CD8 lymphocytes were significantly increased in the lower respiratory tract of patients with COPD. This finding changed the inflammatory concept of COPD by introducing CD8 T lymphocyte into the model.

A histopathological study conducted by Sassetti et al.24 demonstrated that the inflammatory process in COPD occurred in the small airways and lung parenchyma. The bronchioles were blocked by fibrosis and showed infiltration of macrophages and T lymphocytes. The lung parenchyma became distorted and had increased numbers of macrophages and T lymphocytes.

The function of CD8 cells in COPD is not fully known, but there are a few hypotheses. In particular, CD8 cells are said to:

1- be involved in apoptosis and destruction of alveolar epithelial cells, through the release of perforins and tumor necrosis factor α;
2- act as defense against latent viral infection;
3- regulate the immune response to antigen tolerance in the organs; and
4- stimulate the proliferation of collagen fibers, scanned by very late activation antigen 1.

The hypothesis on the presence of CD8+ T lymphocytes in patients with COPD supported that of repeated viral infections, because CD8 cells had been previously known for their cytotoxic capacity. They destroy viral particles and
cells that have been modified by viruses.

The development of the inflammatory/immune theory improved our understanding of COPD and its pathogenesis and has shown new directions for research, one of them being cellular immunity.

Hypothesis on the development of overinflation

In 1924, Letulle described a progressive process whereby the alveolar walls became thinner. He called this process “parenchymal dystrophy.” What we know today is that cellular support structures are fundamental to a 3-dimensional configuration of the alveolar walls. If changed, the alveoli lose their support and begin to break down. Thus, several alveoli units turn into a single unit by modifying the proportional relationship between the alveoli and capillaries, which leads to ventilation perfusion imbalance. This increase in the air space in COPD is progressive and irreversible.

Pathophysiology of COPD

When an individual inhales deeply right after a forced expiration, the volume of air in the lung may increase almost 4-fold. If the lung expansion was uniform, it would take a linear, almost 2-fold increase in the dimensions of the lung. However, the regional differences in the respiratory system limit the possible use of this mathematical analysis. This is partly explained by the pyramid shape of the lungs and the gravitational pressure. The largest expansion occurs in the alveolar duct and alveoli, which keep the angles of the bronchial divisions stable. This is called isotropic expansion.

The lungs contain collagen and elastic fibers. The 2 types form a scaffold-like structural model with more or less distensible fibers that move with respect to one another. (figure 3)

During inspiration, from the residual volume, alveolar ducts expand lengthwise and widen the alveolar lumen. There is an increase in alveolar septal forces, decreasing the deficiencies of the alveolar walls, opening the folds of the septum, and co-opting the alveoli that may be collapsed. This mechanism increases the alveolar surface, facilitating the passage of gas through the alveolar-capillary membrane. This is accompanied by the strengthening and stretching of the alveolar capillaries, which lie in the central parts of the alveolar septum. Thus,
harmonically capillaries if tune on inflation, decreasing the volume of blood that comes in contact with the alveoli, to facilitate gas exchange.

Four components are involved in lumen maintenance of the airway during maximal exhalation: cartilage, elastic fibers, collagen fibers, and surface tension. The air spaces in the lung are not uniform and the preferred direction of the airflow depends on the resistance observed during inspiration and expiration. Gas distribution is affected by gravitational force, contractility of bronchial smooth muscles, and changes in the bronchial wall. The premature collapse of the lung increases the residual volume, which is typically caused by decreased lung elasticity (due to age and COPD), increased bronchial muscle response (in asthma), and increased bronchial wall thickness (in asthma, bronchiectasis, and COPD).

In bronchial bifurcations, the opening of a bronchus may happen before another bronchus. Moreover, small bubbles of fluid move up and down the airways, leading to variable airflow obstruction.

According to the dynamic model of airway closure proposed in 1967 by Mead et al., the equal pressure point theory was the most acceptable for expiratory flow obstruction. The pressure in the alveoli is atmospheric at the end of inspiration and subatmospheric during exhalation. It decreases progressively along the airways up to a point at which there is no more airflow. The flow ceases without a total collapse of the lavage system. Currently, it is assumed that there is balance between extraluminal and intraluminal pressure. In patients with changes in elastic and collagen components and with bronchial wall thickening (e.g., in COPD), the equal pressure point can be observed more distally.

The functional changes of emphysema are related to a decreasing pulmonary area both for gas exchange and as elastic recoil. The respiratory division that occurs during human development determines the design and dimension of the mature lungs.

The airways can be divided into small and large airways. The small airways consist of terminal, transitional, and respiratory bronchioles. The bronchus is divided into 2 smaller branches with smaller diameters, which may have different lengths and extensions. The alveolar sacs are defined as the complex of wells connected to the bronchioles. The inner diameter of the alveolar air sac decreases from 500 to 300 µm. In the symmetric dichotomy of the bronchi, there are 23 bronchial generations. The transverse sectional area of bronchi increases as the division of the airways.

In the large airways, the smooth muscles typically encircle the bronchus, but the cartilage decreases the effects of muscle contraction. From lobar bronchi to bronchioles, the muscles are arranged in the shape of a helix, sometimes along, which also limits the excessive narrowing of the light.

In the small airways

in 1974, Niewoehner et al., and in 1980, Cosio et al. demonstrated that morphological changes in the small airways in COPD showed correlations with lung function. Goblet cell and squamous metaplasia, bronchial ulcers, smooth muscle hyperplasia or hypertrophy, inflammatory cellular infiltrate, interstitial and peribronchial fibrosis, and the deposit of pigments in the airway wall were all considered to be directly related to bronchial obstruction. The first few abnormalities observed in those studies were epithelial changes (squamous metaplasia) and chronic inflammatory infiltrate, with a slight thickening of the connective tissue in the wall of the small airways. With the progression of the disease, the authors found that the cellular inflammatory infiltrate shifted a little, but there was a gradual increase in the amount of connective tissue pigmentation.

Centrilobular and Panlobular Emphysema

In histopathological studies, the destruction of the alveolar wall precedes the enlargement of alveolar spaces, which correlate with the change
in the pressure of pulmonary collapse. Pulmonary damage that occurs in the central area of the lobule is called centrilobular (or centriacinar), and that affecting the entire lobule is known as panlobular (or panacinar).

In 1989, Eildeman et al.28 showed that COPD without α1-antitrypsin deficiency can simultaneously present two types of parenchymal destruction.

In 1991, Kim et al.29 studied 34 patients with COPD who underwent lung resection and showed that the findings of emphysema and pulmonary mechanics were different depending on the affected part of the lobule. Panlobular emphysema was characterized by a more homogenous pattern of destruction and loss of elasticity. In centrilobular emphysema, thickening, destruction, and reduction of light in the bronchioles, leading to increased airway resistance and decrease in elastic recoil were observed. These findings demonstrated that the mechanical properties of the lung are different depending on the type of emphysema since the onset of the disease, accentuating a gradual increase of air space.

Compared to panlobular emphysema, in the centrilobular type, a significant increase in the amount of smooth muscles and small airway fibrosis is observed. In addition, the number of airways smaller than 400 µm in diameter is higher, which correlates with increased airflow resistance in the small airways. These pathological findings show that airflow obstruction in centrilobular emphysema is due primarily to airway abnormalities while reduced elastic recoil plays an additive role. In contrast, in panlobular emphysema, flow limitation is a function of reduced elastic recoil.

In 1973, Anderson and Foraker30 suggested that COPD had different pathogenic pathways. They postulated that the aggression to the lung in panlobular emphysema would be through substances from the bloodstream due to diffuse and homogeneous distribution of emphysema. In centrilobular emphysema, lung destruction is observed in the central area of the alveolar sac and the airway is responsible for distributing harmful substances in the lung.

Epithelial lesions in the lower respiratory tract

The protective barrier of the airway epithelium is broken down by cigarette smoke. The epithelium becomes exposed to ulcers and metaplasia. Numerous studies have shown that smoking modifies epithelial permeability to electron-dense substances, increasing the content of plasma exudation and extending the airways recruiting inflammatory cells (neutrophils, macrophages, and eosinophils). The respiratory epithelium in COPD changes in all stages. Its repair cannot be fully achieved even after smoking cessation and with the use of anti-inflammatory medications such as corticosteroids.

Repair of the lower respiratory tract

Elastin gene expression initiates a repair response after the alveolar injury caused by neutrophil elastase. However, the integrity of the tissue cannot be restored. Smoking changes the regeneration capacity of the airway epithelium. Fibroblasts and epithelial cells release factors (tumor growth factor β, fibronectin) that can modulate and enhance the proliferation of native epithelial cells.

Conclusions

The concept that emphysema results from the proteolysis of the alveolar septum and bronchi has been widely approved in the recent years. The protease–antiprotease hypothesis refers to an episodic or regular release of proteinases that digest proteins in the lung tissue. Under normal conditions, the lungs are protected by the action of protease inhibitors, which originate in the blood but may also be produced locally. Emphysema results from the imbalance in the protease–antiprotease ratio when proteases predominate. As a result, the lung repair is insufficient and functional changes occur. The risk factors described above, including infection
and smoke exposure, are the main determinants of the cellular inflammatory process and oxidative stress. When associated with a genetic predisposition, they may lead to activation of inflammatory cells, CD8+ T lymphocytes, and macrophages, causing progressive parenchymal destruction and thus leading to COPD.

References


