Crit Care Nurs Q
Vol. 44, No. 1, pp. 2–8

Pathophysiology of COPD

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This article provides an overview of the pathophysiology of chronic obstructive pulmonary disease including the physiological mechanisms that are known precursors. The roles of environmental and genetic causes are considered. α_1-Antitrypsin deficiency is also discussed as it relates to the development of airflow obstruction. **Key words:** *α_1-antitrypsin*, *chronic bronchitis*, *chronic obstructive pulmonary disease (COPD)*, *emphysema*, *pathophysiology*

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a disease of pulmonary inflammation and poorly reversible airflow obstruction. It is caused by an immune response to long-term inhalation of particles and gases. In the United States, cigarette smoking is the most common cause; however, pollution and gases have also been implicated. It is a heterogeneous disease with different poorly described phenotypes and both genetic and environmental risk factors. Clinical symptoms, radiologic appearance, and degree of airflow obstruction vary greatly between patients.

PHYSIOLOGIC MECHANISMS

Cigarette smoking and other noxious inhalants cause inflammation in the small airways of all individuals. The immune system has an innate defense system against these toxins. An epithelial barrier provides a physical blockade to foreign materials entering the body through the lungs. Mucociliary clearance removes many inhaled particles that make it past the upper airways. An acute inflammatory response to these foreign molecules removes pathogens from causing further damage, but this response has no memory. The humoral and cellular components of the immune system develop slowly but produce memory to these previous injuries. The tissue is healed through microvascular changes and adding of connective tissue matrix. Both the lung parenchyma and airways are typically affected by this inflammation and remodeling. Differing mechanisms of injury and recovery may lead to chronic bronchitis, emphysema, and bronchiolitis.[1]

Inflammatory mediators and oxidative stress

COPD patients have increased numbers of neutrophils, macrophages, and T lymphocytes (CD8 > CD4) in their lungs. These inflammatory cells release several cytokines and chemotactic factors that cause further inflammation. Macrophages, neutrophils, and epithelial cells release leukotriene B4 that attracts additional neutrophils and T cells. Chemotactic factors such as CXC chemokines, interleukin (IL)-8, and growth-related oncogene α are produced by macrophages and epithelial cells that stimulate cellular migration. Additional

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DOI: 10.1097/CNQ.0000000000000334

proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and IL-1β and IL-6 are released that further perpetuates the inflammatory injury. Growth factors such as transforming growth factor β release connective tissue growth factor that causes scarring and subsequent fibrosis of the lung.[2]

Environmental inhaled toxins such as the free radicals in cigarette smoke produce oxidative stress. In addition to causing the inflammation described earlier, this oxidative stress releases proteases and inactivates several antiproteases. Neutrophils release elastase, cathepsin G, and protease 3, whereas macrophages release cysteine proteases, cathepsins E, A, L, and S, and matrix metalloproteases such as MMP-8, MMP-9, and MMP-12. When these proteases are activated, they cause alveolar wall destruction, mucous hypersecretion, and abnormal tissue repair. Antiproteases typically protect lung tissue and include α_1-antitrypsin (AAT), secretory leucoprotease inhibitor, and tissue inhibitors of metalloproteases, which are inactivated.[2]

Mucus hypersecretion and chronic bronchitis

Long-term inflammation causes metaplasia of the bronchial epithelial goblet cells through inflammation, oxidative stress, protease imbalance, and signal transduction pathways. There are hypertrophy and hyperplasia of submucosal bronchial glands. These cause obstruction to airflow and accelerated decline in lung function, leading to an increase in acute exacerbations. The biochemical properties of the excreted mucus change, making it form more plugs. These mucus plugs block the airways and cause constant colonization of the airway with bacterial pathogens[3] (Figure 1). The amount of phlegm production has been shown to correlate with forced expiratory volume in the first second of expiration (FEV_1) decline over time.[5,6] Patients with chronic bronchitis have lower quality-of-life scores and worse physical limitations.[3,7]

Airflow obstruction and small airway disease

The main areas of airflow obstruction occur at the airways that are less than 2 mm in diameter, or the 4th to 12th generation of bronchi.[1] The narrow diameter of these airways causes inhaled irritants to more easily collide with the bronchial walls and cause damage.[4] On histology, these airways show mucus plugs. They have increased numbers of neutrophils, macrophages, CD4 cells, CD8 cells, B cells, and lymphoid follicles. Thickening of the airways and the number of lymphoid follicles have been shown to correlate with disease progression.[1] There is both a loss of terminal bronchioles and narrowing of these airways. The reduced number and the smaller diameter of airways decrease the total cross-sectional area for airflow, increasing resistance to airflow. This airway destruction of the terminal bronchioles tends to predate the emphysematous changes seen in the alveoli.[8] The emphysematous tissue results in a decreased number of alveolar walls attached to the terminal bronchioles. This can reduce airway patency, making the airways close during expiration and causing airflow obstruction.[4]

On pathology, respiratory bronchiolitis is seen with an increase in macrophages in the lumen of the respiratory bronchioles and alveolar spaces. They contain finely granular golden-brown pigment.[9]

Emphysema

Emphysema is defined as permanent abnormal enlargement of the respiratory airspaces or alveoli accompanied by destruction of the alveolar walls without obvious macroscopic fibrosis.[9] There are 4 main types of emphysema: proximal acinar, panacinar (found in AAT deficiency), distal acinar (or paraseptal), or enlargement with fibrosis (also called paracicatrical emphysema).[9,10] An acinus is the unit of lung tissue that is connected to a single terminal membranous bronchiole. A lobule is the amount of lung tissue that is encompassed by the pleural and/or septa. It

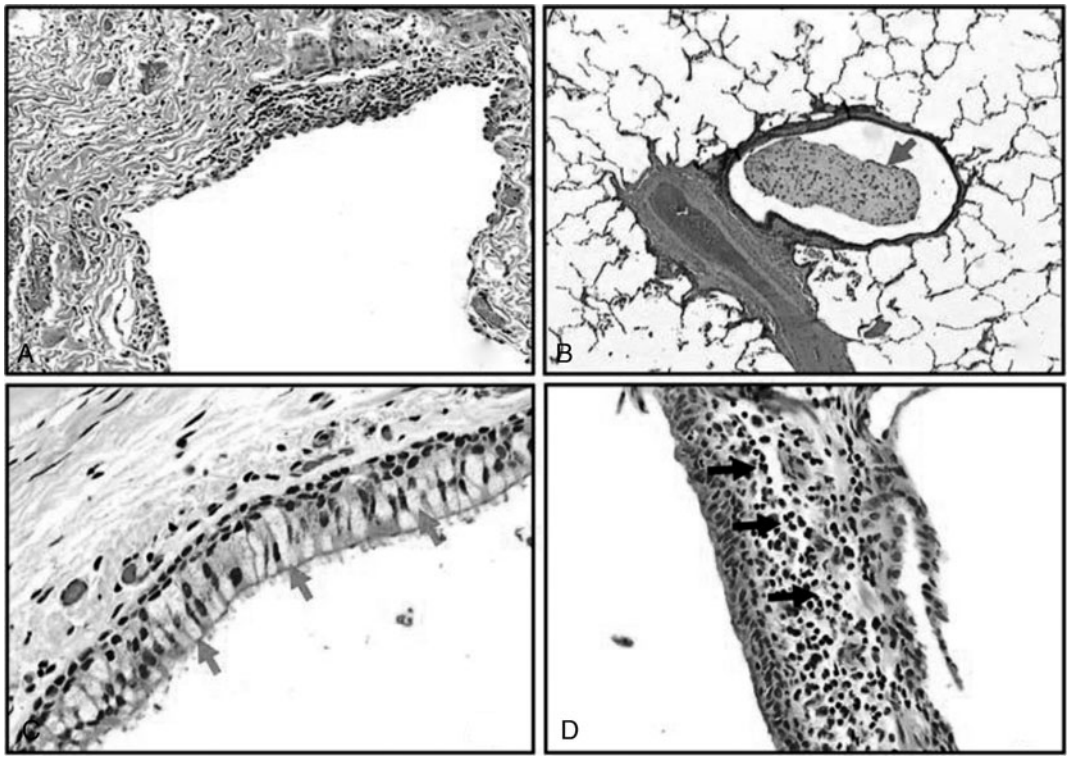

Figure 1. Microscopy of COPD and chronic bronchitis. (A) Masson's Trichrome stain showing fibrosis and thickening of airway. (B) Arrow showing mucus plug in bronchiole. (C) Increased number of goblet cells (arrow) in bronchiole. (D) Increased number of inflammatory cells (arrow) in bronchiole wall. (Reprinted with permission from Higham et al.[4])

typically contains 3 to 6 acini. Proximal acinar emphysema includes the centriacinar emphysema typically seen in cigarette smokers and the focal centriacinar emphysema seen in pneumoconiosis. In centriacinar emphysema, the respiratory bronchioles are affected but the distal alveoli sacs are relatively spared. Because the respiratory bronchioles are in the center of a lobule, the emphysema is centrilobular. Paraseptal emphysema is the opposite, with the distal alveoli affected but with normal proximal acini.[9]

On microscopy, there are increased macrophages and CD8 T lymphocytes. Alveolar walls are destroyed by the loss of epithelial and endothelial cells. Bulla, or emphysematous airspaces measuring greater than 1 cm, may also be seen.[2] This destruction of alveolar walls causes a loss of elastic recoil of the lungs. This leads to airflow obstruction, reduced areas for gas exchange, and increased dead space[2,4] (Figure 2).

Pulmonary vascular changes

Pulmonary hypertension is an important comorbidity of COPD as it is linked to worse mortality and morbidity and typically develops late in COPD. Chronic hypoxia causes pulmonary arterial constriction.[2] There is intimal thickening of the arteries adjacent to the bronchioles due to smooth muscle proliferation and deposition of elastin and collagen. These arteries are unable to dilate fully in response to exercise, acetylcholine, or increases in airflow.[9] Long-term smoking is associated with a decrease in nitric oxide response, further reducing arterial vasodilatation in COPD.[11]

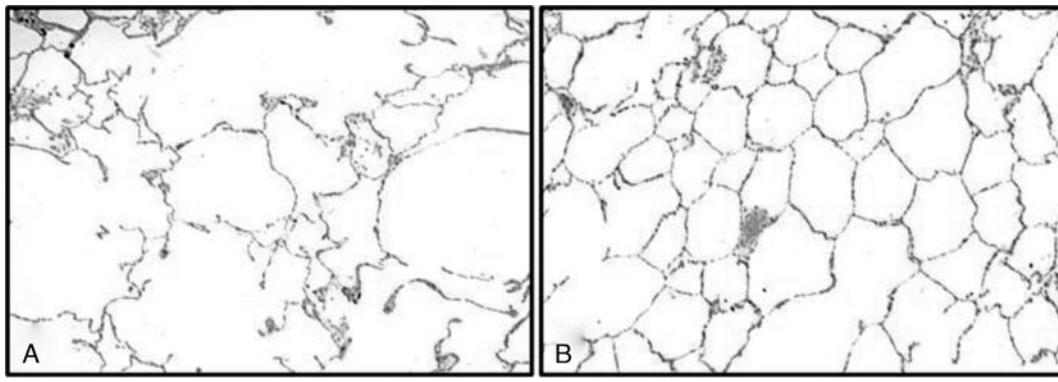

Figure 2. H&E stain. (A) Emphysematous lung with loss of alveolar wall attachments. (B) Normal lung. Reprinted with permission from Higham et al.[4]

Environmental and genetic causes of COPD

Besides cigarette smoking, increases in COPD prevalence have also been associated with environmental pollution, cooking fumes in regions using indoor wood stoves with poor ventilation, exposure to coal and gold mining dust, exposure to gas in cadmium mining, and exposure to dust and gases in underground tunnel workers. The disease is more common among patients with lower socioeconomic status. It has a poorer prognosis when associated with low body mass index (BMI). Even factors in utero or in adolescent development may contribute to future COPD development.[12]

Cigarette smoking is responsible for 80% to 90% of COPD cases in the United States; however, only 15% to 20% of cigarette smokers develop COPD. This suggests that genetic predisposition also plays a large role in the development of COPD. The most important genetic cause is AAT deficiency (see later). Even patients who are heterozygous for this mutation and do not have the disease are at an increased risk of COPD.[12]

There are familial clusterings of COPD in patients with other mutations. Taq-1 polymorphism of AAT is associated with reduced production of AAT and COPD. Mutations in cytokine TNF-α were more prevalent in a group of Taiwanese patients with COPD.[13] Cigarettes contain free radicals that cause oxidative damage to the lungs. Defects in the protective mechanisms for this damage may contribute to COPD. Short tandem repeat polymorphisms in the heme oxygenase-1 gene promoter region[14] and mutations in the glutathione S_1-transferases[15] may be associated with COPD. Multiple other associations of genetic mutations and COPD have been found; however, these genetic variations have not been replicated in other studies. Future research is required to investigate the genetic causes of COPD.[12]

α_1-Antitrypsin deficiency

AAT deficiency is present in 1% to 2% of COPD patients,[16] About 60% of those with AAT deficiency develop airflow obstruction[17] The severity of obstructive lung disease is variable, suggesting that the environment and modifier genes are also clinically important.[16] AAT is a protease inhibitor encoded by the *SERPINA1* gene[18] on chromosome 14q32.1.[16] It is synthesized in the endoplasmic reticulum of liver hepatocytes and then released into the bloodstream. It protects tissue from the enzymes released during inflammation, notably the protease neutrophil elastase. Its levels rise 3 to 5 times in acute inflammation. Symptoms of the disease typically develop between 20 and 40 years of age.[19]

The normal allele encoded by the *SERPINA1* gene is called PI*M (Table). Patients with 2 copies of the normal allele, or PI*MM, will have AAT levels of 100 to 350 mg/dL or 20 to 53 μM in the serum. Pathogenic alleles include PI*S, PI*Z, and the Null allele (or nonfunctional gene). The Z allele is caused by a single substitution of lysine for glutamic acid at position 342. This causes polymerization of the protein that accumulates in the endoplasmic reticulum of hepatocytes. When heterozygous (PI*ZZ), this causes severely low AAT levels and a high risk of cirrhosis.[19] The majority of patients with AAT deficiency have the genotype PI*ZZ and will have AAT levels below 50 mg/dL or 11 μM/L, which is considered the protective threshold.[16] The Z allele is more common in those with European descent, where the S allele is more common in those with Mediterranean descent. Other more rare alleles exist, including the Pittsburgh allele, where AAT is converted from an elastase inhibitor to a thrombin inhibitor.[19] These patients are prone to bleeding issues.[16]

AAT deficiency has been implicated as a possible cause of COPD, bronchiectasis, atopic disease, liver cirrhosis, hepatocellular carcinoma, ANCA vasculitis (mainly granulomatosis with polyangiitis and microscopic polyangiitis), necrotizing panniculitis, glomerulonephritis, abdominal aortic aneurysms, intracranial aneurysms, pancreatic islet cell tumors, pancreatitis, and celiac disease.[17]

Early diagnosis of AAT deficiency allows for lifestyle modification, mainly avoiding inhaled toxins. However, it is estimated that only 10% of patients with AAT deficiency have been identified. The average age of diagnosis is 43.9 years, and there is an average delay of diagnosis of 5.6 $\pm$ 8.3 years.[19] In a combined statement from 2003, the American Thoracic Society and the European Respiratory Society recommend considering AAT deficiency in patients with (1) early-onset emphysema (age $\leq$45 years), (2) emphysema in the absence of a recognized risk factor, (3) emphysema with prominent basilar hyperlucency, (4) otherwise unexplained liver disease, (5) necrotizing panniculitis, (6) antiproteinase 3–positive vasculitis (C-ANCA), (7) family history of emphysema bronchiectasis liver disease or panniculitis, and (8) bronchiectasis without obvious cause. Siblings of patients with AAT deficiency should be screened. Screening may be considered in adolescents with asthma and a nonreversible airflow obstruction. There are currently no recommendations for population screening.[17]

Patients with AAT deficiency should have typical COPD care, including avoiding cigarette and environmental pollutants, influenza and pneumococcal vaccination, bronchodilators, inhaled steroids, oxygen

Table. Genotype of AAT and Risk of Emphysema and Cirrhosis[a]

Genotype	Serum Level AAT, mg/dL (μm/L)	Risk of Emphysema	Liver Accumulation	Risk of Cirrhosis
MM	Normal 150-350 (20-48)	Normal	No	Normal
Null-Null	Undetectable	Greatest risk	No	Normal
ZZ	20-45 (2.5-7)	High (60%)	Yes	High (30%-40% adults)
SZ	45-120 (8-16)	Slightly increased	Yes	Slightly increased
SS	100-200 (15-33)	Possible	Small amount	No increase
MZ	90-210 (17-33)	Possible	Yes	Slightly increased

Abbreviation: AAT, α_1-antitrypsin.

[a]From American Thoracic Society and European Respiratory Society.[17]

as needed for desaturation, and exercise. Intravenous (IV) human plasma-derived augmentation therapy is the IV administration of purified human AAT concentrate. Adverse reactions are rare and include fever, chills, dyspnea, and anaphylaxis. Augmentation benefit is approved for individuals with AAT deficiency and emphysema with a confirmed airflow obstruction of any severity. This has been proven to slow the rate of FEV_1 decline and decrease mortality. It has the strongest benefit in patients with moderate airflow obstruction or FEV_1 35% to 60% of predicted.[17]

Systemic inflammation in COPD

Patients with COPD are also at risk for cachexia, muscle wasting, cardiovascular disease, anemia, secondary polycythemia, osteoporosis, diabetes, depression, anxiety, lung cancer, and sleep apnea.[2] There are increased systemic inflammatory markers in COPD such as cytokines, chemokines, and acute-phase proteins. This may be from smoking or from the disease itself. These markers are higher in times of exacerbation or with severity.[18]

IL-6 is elevated in COPD, particularly during exacerbations, and may increase C-reactive protein and other acute-phase proteins from the liver. Increases in IL-6 may be associated with cardiac failure and skeletal muscle weakness.[18,20] TNF-α is elevated in COPD and has also been implicated as a cause for cachexia.[18,21] The loss of type 1 muscle fibers has been shown to correlate with worsening dyspnea scores.[22]

COPD and heart disease share many risk factors, especially smoking. However, the pulmonary disease also affects heart function. FEV_1 is an independent predictor for the mortality from a myocardial infarction even when adjusted for cigarette smoking.[23] The systemic inflammation in COPD has been implicated as a possible cause for atherosclerotic disease.[18]

Up to 75% of patients with COPD may have osteoporosis. The severity of COPD correlates with the severity of the bone mineral density loss. The bone mineral density loss also correlates with loss of muscle mass.[24] Smoking, low BMI, and steroids use put patients at risk of osteoporosis and are also present in many with COPD. However, emphysema itself may also contribute to osteoporosis.[18] Thoracic vertebral compression fractures from osteoporosis may, in turn, worsen lung function.[25]

COPD shares several risk factors with lung cancer and obstructive sleep apnea. The systemic inflammation may also increase the risk of these diseases. It is important to screen patients for these comorbidities.[18]

Pathophysiology of COPD exacerbations

COPD exacerbations may be caused by bacterial or viral infection, air pollution, and changes in the weather. They are associated with an increased number of neutrophils and sometimes increased eosinophils in the lungs. Inflammation in the lungs may cause edema, mucus hypersecretion, and bronchoconstriction. This along with respiratory muscle fatigue may worsen gas exchange. Worsening oxygenation may lead to worsening perfusion due to autoregulation of pulmonary vasculature. This may increase pulmonary vasculature pressures and lead to right ventricle volume overload. Respiratory muscle fatigue and diminished alveolar ventilation from obstruction also causes worsening hypercapnia and respiratory acidosis and eventually may cause death.[2]

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