

Airway Clearance Indications in Chronic Obstructive Pulmonary Disease: An Overview

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Chronic obstructive pulmonary disease (COPD) is a disease process characterized by progressive, irreversible airway obstruction and destruction of the pulmonary parenchyma. As a result, the ability of the lungs to perform ventilation is diminished. Pathological features include distention of interstitial tissues by gas or air, resulting in destructive changes in the pulmonary parenchyma.

COPD is not a primary disease entity. Rather, it is an umbrella categorization of complex, often mixed pathologies including chronic bronchitis,¹ pulmonary emphysema,² chronic asthma, and chronic bronchiolitis. The most prominent disease process may occur within the airways or within the lung parenchyma. Although the pathophysiology of airflow obstruction is different in each of these disorders, patients frequently demonstrate features of two or more underlying conditions. The broad term COPD is used to designate a condition that defies more precise classification; the concept of COPD as a diagnostic category continues to evolve and remains controversial.^{3,4}

Epidemiology

COPD ranks among the leading causes of adult morbidity and mortality worldwide. Because COPD is not a clearly standardized diagnosis, specific data are difficult to interpret. However, an estimated 16 million Americans have the disease.⁵ With approximately 85,000 deaths annually, COPD places fourth as a cause of death in the United States.^{6,7}

The costs of COPD are enormous.^{8,9} The economic burden upon the health care system, society at large, and affected patients and their families is staggering. Costs, both economic and human, associated with medical and auxiliary care, loss of livelihood, diminished quality of life and reduced life expectancy cannot be estimated. As knowledge of the pathophysiology of COPD expands, as awareness of the enormous social and economic impact of COPD grows, and as the success of smoking cessation strategies improves, it is realistic to hope that this public health epidemic can be controlled.

Pathophysiology

Because COPD typically includes elements of both chronic bronchitis and emphysema, the pathophysiology of COPD is highly idiosyncratic. Understanding of the disease process must acknowledge the greater or lesser role of these and other underlying pathologies.

- Chronic bronchitis is characterized by enlargement and multiplication of the mucous glands, resulting in increased airway mucus production. In chronic bronchitis, evidence suggests that not only is the quantity of mucus increased, but its composition may be altered as well, becoming abnormally viscous. Moreover, bronchial walls show evidence of an

inflammatory process with cellular infiltration and variable degrees of fibrosis.

- Emphysema, in simple terms, is a pathological distention of interstitial tissues by gas or air, and subsequent destruction of alveolar walls. Several subtypes of emphysema are recognized,¹⁰ but the centrilobular form, in which predominant involvement and dilation occurs in the respiratory bronchioles, is the most important factor in precipitating airflow obstruction.

COPD affects the bronchi, the bronchioles, and the pulmonary parenchyma. The pathophysiological consequences resulting from disease at each of these levels contribute to the overall clinical picture of COPD.¹¹ Therefore, to understand the pathophysiology of COPD, it is useful to review structure-function correlations for each of these aspects of COPD:¹²

- To the extent that chronic bronchitis is present, structural alterations in mucus-secreting glands in the bronchi result in mucus hypersecretion and alterations in mucus characteristics;
- Also in the presence of chronic bronchitis, hypersecretion and inflammation of the bronchi and bronchioles contribute to airflow obstruction by effecting corresponding decreases in the caliber of airways;
- Inflammation and emphysemic fibrosis in the bronchioles further restrict airflow¹³; and
- In the pulmonary parenchyma, emphysemic destruction of alveolar walls and consequent loss of

elastic recoil results in decreased expiratory flow rates because:

- 1) a reduced driving pressure is available for expiratory airflow; and
- 2) damaged alveolar walls diminish the traction exerted by supporting tissues from the pulmonary parenchyma, thus promoting airway collapse during expiration.

Other pathophysiological manifestations of COPD, including specific abnormalities in pulmonary function, the mechanisms of gas exchange, and pulmonary hypertension, while crucial to an understanding of the disease state, fall outside the scope of this discussion of airway clearance indications.

Etiology: Tobacco Smoking and COPD

Cigarette smoking, both active and passive, is believed to be the major etiological factor in the development of COPD.^{14,15} Investigations of other factors, including air pollution (occupational or urban),¹⁶ infection (especially during early childhood),¹⁷ and genetics,¹⁸ suggest that these might modify host response to cigarette smoke.^{19,20} Because only 10-20% of smokers develop severe COPD, other factors in addition to those cited, such as socioeconomic status, diet and nutrition, climate, and nonspecific airway hyper-responsiveness,²¹ may modify risk.

Smoking affects the lung at various loci: the bronchi, the bronchioles, and the lung parenchyma. The effect of tobacco smoke in the larger airways (i.e. the bronchi) alters both the structure and function of the bronchial mucous glands. Exposure to smoke increases both the number and size of these mucus-secreting glands, resulting in the production and deposition of excess mucus within the lumen of the airway. In response to enlarged, hyperactive mucous glands, as well as to the influx of inflammatory cells, airway walls become thickened. Correspondingly, the diameter of the airway lumen is reduced and may more easily become congested or plugged with mucus.

Tobacco smoke also induces structural changes in airway cilia. Studies of the effects of chronic smoking on ciliary ultrastructure have demonstrated the development of numerous specific and non-specific morphological changes, which occur in proportion to the duration and dose of tobacco exposure.²² Abnormal cilia are frequently dyskinetic with an ineffective stroke²³ and thereby participate in the impairment of secretion clearance.

Smoking also damages small airways. Exposure to smoke results in bronchiolar narrowing, inflammation and fibrosis. These changes are thought to explain much of the airflow obstruction seen in patients with mild COPD. Tobacco-related damage to pulmonary parenchyma results in the eventual development of emphysema. The pathophysiology of emphysema is complex. Current thought favors the protease-antiprotease hypothesis of the association between smoke exposure and destruction of the alveolar walls.²⁴ Simply expressed, emphysema is a consequence of the destruction of the connective tissue matrix of the alveolar walls by proteolytic enzymes. These enzymes, called proteases, are released by inflammatory cells in the alveoli and break down elastin, a protein important for the structural integrity of the alveolar walls. The pathologic changes of emphysema appear in proportion to the elastolytic activity of such enzymes.^{25,26}

Clinical Features

In mild COPD, symptoms are insidious and typical patients do not seek medical help until they experience an acute exacerbation. In early disease, cough and the production of mucoid or purulent sputum are common; in advanced disease, breathlessness, often severe, accompanies even slight physical exertion. Persons with COPD typically demonstrate less than 50% normal lung function.^{27,28} There may be concomitant asthma or congestive heart failure with characteristic bronchospasm. In addition to chronic symptoms, disease progression is punctuated by episodes of acute exacerbation, most commonly triggered by viral or bacterial respiratory infections or exposure to air pollutants.

In the diagnosis of COPD, the following symptoms are clinically significant:

- **Cough:** Cough is an important respiratory defense mechanism, functioning both to clear the airways of excess mucus and to clear and protect airways from foreign particles, including pathogens. In COPD, frequent, sometimes convulsive coughing may result in episodes of severe breathlessness. In advanced COPD, severe cough may have serious consequences. Syncope, or fainting, may occur when there is an acute rise in intrathoracic pressure during the expiratory phase of the cough, producing a transient reduction in venous return and reduced cardiac output. Moreover, the high intrathoracic pressures which develop during prolonged bouts of coughing are sometimes sufficient to fracture one or more ribs (“cough fractures”), especially in immobile patients and/or those treated with corticosteroids.²⁹ It is uncertain whether cough in COPD is chiefly a physiological response to mucus

hypersecretion or a result of specific pathological alterations in the airways.³⁰

- **Mucoid or purulent sputum:** In symptomatic COPD patients, alterations in the mucus-secreting glands result in increased sputum production and impaired secretion clearance. During infectious exacerbations, the usual colorless sputum may, as a function of the inflammation, become purulent. The physiochemical properties of infectious sputum demonstrate rheological changes in viscosity, which promote secretion retention.
- **Breathlessness (dyspnea):** Chronic breathlessness is the most clinically important feature of COPD. Patients experience chronic ventilation-perfusion (V/Q) mismatch as a result of mechanisms associated with emphysema, chronic bronchitis, or a combination of underlying pathologies. The resulting breathlessness reflects decreased pulmonary function and is associated with poor prognosis.³¹ As breathlessness progresses, patients rely increasingly upon accessory muscle groups to support ventilation. If these muscle groups are required for other physical activities, the degree of breathlessness increases dramatically.³²
- **Acute exacerbation:** The clinical course of COPD is punctuated by episodes of acute exacerbation that increase in frequency and severity as the condition progresses. During an acute exacerbation, worsening V/Q mismatch is related to partially reversible pathophysiological abnormalities of airway narrowing, such as mucus plugging, bronchial wall edema, bronchoconstriction, and overinflation and/or air trapping.³³ Some patients may require assisted ventilation.

The Role of Mucus in COPD

COPD is a complex, variable, and incompletely understood diagnostic entity. Mucus is one of many important components in the overall pathophysiology. Mucus hypersecretion is a manifestation of glandular or goblet cell hypertrophy in the airway wall as a response to noxious exposure. The presence of excess mucus may affect pulmonary function, pulmonary health and survival in several ways:

- **Pulmonary Function:** Chronic mucus hypersecretion is strongly associated with FEV₁ decline in COPD. The magnitude of decline is increased proportional to degree of mucus hypersecretion, thus supporting the concept of a causal role of chronic mucus hypersecretion in COPD.³⁴

- **Airway Obstruction:** Mucus hypersecretion in COPD results in accumulation in central and peripheral airways, contributing significantly to airway obstruction. As a consequence of the pathophysiological changes described earlier, including ciliary impairment, increased airway resistance, and reduced elastic recoil, the smaller airways in particular are prone to secretion retention and mucus plugging.³⁵
- **Mucociliary Function:** The ability of the mucociliary apparatus to clear secretions is seriously compromised in COPD as a result of:³⁶

Ciliary dysfunction: Structural damage to the cilia is caused by exposure to tobacco smoke.³⁷ In addition to morphological changes, ciliary function may decrease.

Mucus: Changes in the rheological properties of mucus occur as a result of exposure to tobacco smoke and of chronic bronchial infection and inflammation. Chemical and physical alterations render such mucus thicker, more tenacious, and therefore less easily cleared by either ciliary action or cough.

- **Risk of Infection:** Mucus hypersecretion and retention favors the development of bacterial colonization with recurrent bronchial infection, pneumonia, and, ultimately, respiratory failure.³⁸
- **Morbidity and Mortality:** A significant association has been demonstrated between mucus hypersecretion and increased illness and death among patients with COPD.^{39,40}

In a recent long-term study of nearly 10,000 individuals, chronic mucus hypersecretion was strongly and consistently associated with increased frequency of hospitalization because of COPD.⁴¹

In another study, involving nearly 14,000 subjects followed for 10 years, chronic mucus hypersecretion in persons with COPD-related ventilatory impairment was associated with a significantly poorer prognosis.⁴²

Need for Airway Clearance Therapy

The complexity of COPD as a diagnostic entity cannot be overemphasized. Individuals with COPD represent a heterogeneous population and manifest a broad spectrum of clinical and pathophysiological characteristics. Among a large subset of COPD patients, chronic bronchitis is a prominent feature of the illness. Patients who suffer from excessive pulmonary secretions are susceptible to mucus plugging and recurrent pulmonary infection. Recurrent

infection may affect the clinical course of COPD as follows:⁴³

- 1) Recurrent acute infectious exacerbations accelerate the lung damage associated with COPD;
- 2) Acute exacerbations are themselves associated with morbidity and mortality;
- 3) Chronic colonization/infection of the lower respiratory tract contributes to cyclical progressive lung damage;
- 4) Pulmonary infection and mucus plugging contributes to V/Q mismatching and often result in hypoxia;
- 5) Acute hypoxia causes dyspnea and can affect global health, including the cardiovascular and nervous systems; and
- 6) Chronic hypoxia can result in pulmonary hypertension and cor pulmonale (right heart failure).

For COPD patients in whom airway secretions cause significant symptoms, airway clearance therapy is recommended to help mobilize and clear retained secretions.^{44,45,46} Effective airway clearance therapy helps prevent infection, improves oxygenation, and slows the progressive pulmonary deterioration associated with COPD.

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¹The definition of chronic bronchitis remains functional, but many clinicians believe the diagnosis requires the presence of a specific type of mucosal inflammation.

²The morphological definition of emphysema as destructive enlargement of peripheral air spaces is widely accepted.

³The most up-to-date definition of COPD, provided by the European Respiratory Society in the development of its 1998 monograph devoted to the condition, is expressed in simple functional terms: "COPD is a condition characterized by reduced maximum expiratory airflow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment. The only positive requirement for a diagnosis of COPD is abnormal spirometry, but there are many other causes of airway obstruction. By convention, extrathoracic airway obstruction, localized forms of intrathoracic airway obstruction (e.g. bronchial carcinoma) and most specific causes of widespread obstruction of intrathoracic airways (e.g. cystic fibrosis) are excluded. These exclusions emphasize the uncertain etiology of COPD, although in Westernized countries, smoking is a predominant influence." Pride NB, Vermeire P. Definition and differential diagnosis. In: *Management of Chronic Obstructive Pulmonary Disease, European Respiratory Monographs* Vol. 3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.

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¹¹In addition, the degree of airway reactivity, determined in part by environmental and genetic factors, appear to modify the clinical expression of the disease in individual patients.

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²⁵Elastase, an important proteolytic enzyme, is released by both polymorphonuclear cells (PMNs) and alveolar macrophages. Both cells occur in smoker's lungs in increased numbers in response to episodes of inflammation and because they are recruited to lung tissues by oxidants present in cigarette smoke. In healthy lungs, an elastase inhibitor called alpha 1 antitrypsin is believed to maintain a balance between elastase and its inhibitor to prevent uncontrolled destruction of the alveolar wall. When this balance is upset, as occurs frequently in smokers, either by an increase in elastase released as a result of inflammation or by a decrease in antielastase activity caused by the oxidation of a critical amino acid residue of alpha 1-antitrypsin at or near the site where protease inhibitor binds to elastin, the development of emphysema is accelerated. *Ibid*.

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