

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.

References

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.

⁴In the definition of COPD, the most contentious issue concerns the inclusion of asthma with persistent airway obstruction. Although the European Respiratory Society, after discussion, chose to exclude this subgroup of asthma, it is explicitly included in the 1995 statement of the American Thoracic Society. American Thoracic Society. Standards

for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S77-S120.

⁵Beers MH, Berkow R, eds. Chronic obstructive airway disorders. *The Merck Manual of Diagnosis and Therapy* 17th ed. Whitehouse Station, NJ: Merck & Co, 1999. 568-582.

⁶Roche N, Huchon GJ. Current issues in the management of chronic obstructive pulmonary diseases. *Respirology* 1997; 2(3): 215-229.

⁷In 1989, Feinleib et al. comprehensively reviewed mortality data from the U.S. and demonstrated a relatively persistent overall trend in deaths from 1950-1985, during which period the overall mortality from all COPD increased approximately fourfold. Absolute mortality rates in individuals aged 55-84 years in 1985 were approximately 200/100,000 for males and 80/100,000 for females. The dramatic increase in the incidence of COPD cannot fully be explained by improved diagnosis and record keeping. Feinlieb M, Rosenberg HM, Cillons JG, Delozier JE, Pokras R, Chevarley FM. Trends in COPD morbidity and mortality in the United States. *Am Rev Respir Dis* 1989; 140: S9-S18.

⁸Cydulka RK, McFadden ER, Emerman CL, Sivinski LD, Pisanelli W, Rimm AA. Patterns of hospitalization in elderly patients with asthma and chronic obstructive pulmonary disease. *Am Respir Crit Care Med* 1997; 156: 1807-1812.

⁹*Trends in Chronic Bronchitis and Emphysema: Morbidity and Mortality.* (American Lung Association, Epidemiology and Statistics Unit March 1998).

¹⁰Among types of emphysema, two forms are clinically prevalent. Panlobular (panacinar) emphysema occurs in patients with alpha-1 antitrypsin deficiency and involves relatively uniform, diffuse damage. Centilobular (centriacinar) emphysema is characterized by irregular damage, with concentration of airspace enlargement at the level of respiratory bronchioles.

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.

¹²Rodriguez-Roisin R, MacNee W. Pathophysiology of chronic obstructive pulmonary disease. In: *Management of Chronic Obstructive Pulmonary Disease, European Respiratory Monographs* Vol. 3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.

¹³Stanescu D. Small airway disease and chronic obstructive pulmonary disease. In: *Management of Chronic Obstructive Pulmonary Disease, European Respiratory Monographs* Vol.3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.

¹⁴Davis RM, Novotny TE. The epidemiology of cigarette smoking and its impact on chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140 (3 pt 2): S82-S84.

¹⁵Burchfiel CM, Marcus EB, Curb JD, Maclean WM, et al. Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. *Am J Respir Crit Care Med* 1995; 151: 1778-1785.

¹⁶Hendrick DJ. Occupation and chronic obstructive pulmonary disease (COPD). *Thorax* 1996; 51: 947-952.

¹⁷Shaheen SO, Barker DJP, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1995; 151: 1649-1652.

¹⁸Snider GL. Pulmonary disease in alpha-1-antitrypsin deficiency. [Editorial] *Ann Int Med* 1989; 111: 957-959.

¹⁹U.S. Department of Health and Human Services, 1984. The health consequences of smoking: chronic obstructive lung disease. A report of the Surgeon General U.S. Department of Health and Human Services, Office on Smoking and Health. USGPO, Washington, D.C. DHHS Publication No. (PHS) 84-50205.

²⁰Studies of various factors implicated in the etiology of COPD are numerous; results are equivocal, and their slight significance has been distorted and exploited to detract from the overwhelming risk of developing COPD caused by cigarette smoking. For example, there is good evidence that some dietary factors, particularly antioxidant vitamins C and E, fish oils, and magnesium, may combat inhaled oxidizing agents such as those of tobacco smoke. The sale of antioxidant

agents by health food stores has become a growth industry, but the modest protection offered by such supplements is of little value to smokers.

Bast A, Haenen GR, Doleman CJ. Oxidants and antioxidants: state of the art. *Am J Med* 1991; 91: 2S-13S.

²¹O'Connor GT, Sparrow D, Weiss ST. The role of allergy and non-specific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225-252.

²²Such anomalies include giant cilia with complete or incomplete axonemes, a lack of either peripheral or central doublet microtubules, and compound cilia. Verra F, Escudier E, Lebarry F, et al. Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and nonsmokers. *Am J Respir Crit Care Med* 1995; 151: 630-634.

²³Rossmann CR, Lee RM, Forrest JB, Newhouse MT. Nasal ciliary ultrastructure and function in patients with primary ciliary dyskinesia compared with that in normal subjects and in subjects with various respiratory diseases. *Am Rev Respir Dis* 1984; 129: 161-167.

²⁴Pierce JA. Antitrypsin and emphysema: perspectives and prospects. *JAMA* 1988; 259: 2890-2895.

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*.

²⁶Compared with non-smokers, the lower airways of smokers consistently yield five to ten times as many alveolar macrophages when lavaged. Moreover, metabolically activated inflammatory cells including PMNs are abundant in the lungs of smokers, releasing proteolytic enzymes capable of destroying lung tissue. Hoidal JR, Jeffrey PK. Cellular and biochemical mechanisms in chronic obstructive pulmonary disease. In: *Management of Chronic Obstructive Pulmonary Disease, European Respiratory Monographs* Vol. 3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.

²⁷Postma DS, Rees PJ. Management of stable COPD. *Eur Respir Mon* 1998; 7: 247-263.

²⁸Khan MG, Lynch III JP, eds. *Pulmonary Disease Diagnosis and Therapy: A Practical Approach*. Baltimore: Williams and Wilkins, 1997. 207.

²⁹Calverley PMA, Georgopoulos D. Chronic obstructive pulmonary disease: symptoms and signs. In: *Management of Chronic Obstructive Pulmonary Disease, European Respiratory Monographs* Vol. 3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.

³⁰*Ibid*.

³¹O'Donnell DE, Bertley JC, Chan LKL, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation. *Am J Respir Crit Care Med* 1997; 155: 109-115.

³²Kirby RL. Dysynchronous breathing during arm but not leg exercise in patients with chronic airflow obstruction. *N Engl J Med* 1986; 314: 1485-1490.

³³Rodriguez-Roisin R, et al. *Op cit* (n.12).

³⁴Vestbo J, Prescott E, Lange P, et al. Association of chronic mucus hypersecretion with FEV₁ decline and chronic obstructive pulmonary disease morbidity. *Am J Respir Crit Care Med* 1996; 153: 1530-1535.

³⁵Aikawa T, Shimura S, Sasaki, H, et al. Morphometric analysis of

intraluminal mucus in airways in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: 477-482.

³⁶Wanner A. The role of mucus in chronic obstructive pulmonary disease. *Chest* 1990. 97 (2): 11S-15S.

³⁷Verra F, et al. *Op cit* (n. 22).

³⁸Jansen HM, Sachs AP, van Alphen L. Predisposing conditions to bacterial infections in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 151 (6): 2073-2080.

³⁹Presto E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J* 1995; 8 (8): 1333-1338.

⁴⁰Annesi I, Kauffman F. Is respiratory mucus hypersecretion really an innocent disorder? A 22 year mortality survey of 1,061 working men. *Am J Respir Dis*. 1989; 134: 688-693.

⁴¹Vestbo J, et al. *Op. cit* (n. 34).

⁴²Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; 45: 579-585.

⁴³Murphy TF, Sethi S. Bacterial infection in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 146: 1067-1083.

⁴⁴Roche N. *Op cit* (n.6).

⁴⁵Chronic Obstructive Pulmonary Disease. In Weinberger SE, ed. *Principles of Pulmonary Medicine*, 3rd edition. Philadelphia: WB Saunders, 1998.

⁴⁶Decramer M, Donner CF, Schols AM. Rehabilitation. In: *Management of Chronic Obstructive Pulmonary Disease, European Respiratory Monographs* Vol. 3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.