ОБЗОРЫ ЛИТЕРАТУРЫ

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РЕЗЮМЕ

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ОЦЕНКА БРЕМЕНИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ (ХОБЛ) И РОЛИ РАННЕЙ ДИАГНОСТИКИ ДЛЯ ЭФФЕКТИВНОГО ЛЕЧЕНИЯ ЭТОГО ЗАБОЛЕВАНИЯ

(Обзор литературы)

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В данной статье представлен обзор литературы по бремени Хронической обструктивной болезни легких (ХОБЛ) в разных странах мира. Описаны данные по эпидемиологии, патогенезу, факторам риска, генетической предрасположенности, патофизиологии, клинико-функциональной манифестации и лечении ХОБЛ.

Ключевые слова. *Хроническая обструктивная болезнь легких, эпидемиология, патогенез, факторы риска, клинико-функциональная манифестация, лечение.*

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ХУЛОСА

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АРЗЁБИИ БЕМОРИИ МУЗМИНИ ОБСТРУКТИВИИ ШУШ (БМОШ) ВА НАҚШИ ТАШХИСИ БАРВАҚТ БАРОИ ТАБОБАТИ САМАРАНОК (Шарҳи адабиёт)

Факултаи тиббии донишгоҳи Балх, Мазори Шариф, Афғонистон,
Кафедраи фтизиопулмонологияи МДТ ДДТТ ба номи Абуалӣ ибни Сино, Тоҷикисоон

Дар мақолаи мазкур баррасии адабиёт оид ба бори бемории музмини обструктивии шуш (БМОШ) дар саросари ҷаҳон пешниҳод шудааст. Маълумот дар бораи эпидемиология, патогенез, омилҳои хавф, майли генетикӣ, патофизиология, зуҳуроти клиникӣ ва функсионалӣ ва табобати БМОШ тавсиф шудааст.

Калимаҳои калидӣ: *Бемории музмини обструктивии шуш, эпидемиология, патогенез, омилҳои хавф, зуҳуроти клиникӣ ва функсионалӣ, табобат.*

ABSTRACT

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ASSESSING THE BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND THE ROLE OF EARLY DIAGNOSIS FOR EFFECTIVE TREATMENT OF THIS DISEASE

(Literature review)

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This article presents a literature review on the burden of chronic obstructive lung disease (COPD) worldwide. It describes data on the epidemiology, pathogenesis, risk factors, genetic predisposition, pathophysiology, clinical and functional manifestations, and treatment of COPD.

Keywords: *Chronic obstructive lung disease, epidemiology, pathogenesis, risk factors, clinical and functional manifestations, treatment.*

COPD is the name of a group of chronic and slowly progressive respiratory disorders characterized by reduced maximal expiratory flow during forced exhalation. Most of the airflow obstruction is fixed, but a variable degree of reversibility and bronchial hyper reactivity may be seen. COPD may coexist with asthma and, when abnormal airway reactivity is present, differentiation between these disorders can be challenging. COPD comprises emphysema and chronic bronchitis, two distinct processes, although most often present in combination. The definition excludes other causes of chronic airflow obstruction such as cystic fibrosis. bronchiolitis obliterans and bronchiectasis [1, 3,12, 18].

Emphysema is defined anatomically as a permanent and destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis and with loss of normal architecture [8, 17, 18, 21].

Chronic bronchitis is defined clinically as the presence of a cough productive of sputum not attributable to other causes on most days for at least 3 months over 2 consecutive years. Chronic bronchitis may be present in the absence of airflow limitation, but COPD always involves clinically significant airflow limitation [10, 18, 23, 25].

COPD is a common medical problem affecting an estimated 16 million Americans. Males are more frequently affected than females, and Caucasians more frequently than African Americans. There is a higher prevalence of COPD among persons with a lower socioeconomic status and in those with a history of low birth weight. COPD is the fourth leading cause of death in the United States and is the only one of the 10 leading causes of death for which mortality rates are still rising. Prevalence peaks in the seventh and eighth decades, then levels off, largely due to mortality [18, 23, 29, 33].

COPD MECHANISMS OF PATHOGENESIS

COPD devolves from an inflammatory process involving the airways and distal airspaces. Increased activity of oxidants combined with decreased activity of antioxidants, termed oxidative stress, have been implicated in the development of inflammation and COPD. Cigarette smoke produces high concentrations of oxygen free radicals including superoxide, hydrogen peroxide, and hypo-chlorous acid. Cigarette smoke is an independent source of Fe2+, releases Fe2+from ferritin, and catalyzes the formation of the highly active hydroxyl radical from O2-and H2O2by eosinophils, neutrophils, and alveolar macrophages. Cigarette tar contains nitric oxide and induces nitric oxide synthase. In the presence of oxidants, NO is metabolized to cytotoxic peroxynitrates. In order for elastase to degrade elastin, a1antitrypsin (a1AT) must be inactivated. Cigarette smoke, oxidants, activated neutrophils, and type II alveolar pneumocytes are all capable of inactivating a1AT as well as matrix metalloproteinase inhibitors. Oxidant stress is also capable of inducing mucus hypersecretion. Cigarette smoke also acts as a chemoattractant and upregulates adhesion molecules. Smoke increases neutrophil transit time through the pulmonary circulation, increases adhesion, and decreases deformability. Smoke and elastase both increase the expression of the pro-inflammatory nuclear transcription factor kB (NfkB) as well as interleukin 8, a chemokine found to be elevated in COPD patients that recruits neutrophils, basophils, eosinophils, and T lymphocytes. The submucosa of the small airway in patients with COPD has increased numbers of CD8 lymphocytes and eosinophils, macrophages, and mast cells. Neutrophils are increased in smokers, but their numbers do not correlate with the presence of airflow obstruction. Patients with chronic airflow obstruction show higher levels of myeloperoxidase and

eosinophilic cationic protein than do patients with normal airflow. Macrophages and mast cells produce transforming growth factor b (TGF-b), a peptide related to fibrogenesis. Patients with chronic airflow obstruction show a twofold elevation of TGF-b in lavage liquid; the amount of TGF-b shows a significant negative correlation with FEV1 (the forced expiratory volume in 1 s). Smoke also leads to lipid peroxidation and to DNA damage. Widespread point mutations of the p53 gene locus have been identified in patients with lung cancer and precancerous dysplasia. These may predispose to the development of lung cancer [18, 31, 34, 19].

RISK FACTORS OF COPD

COPD is characterized by a reduced FEV1and an accelerated rate of decline of FEV1. The reduction in FEV1 can occur by any of three pathways: (1) impaired childhood growth and development, with a lower peak in early adulthood and a normal rate of decline with aging (e.g., early childhood infection and passive smoke exposure); (2) normal growth and development with a premature peak but normal subsequent decline (e.g., asthma and passive smoking); and (3) normal growth and development and peak with accelerated decline (e.g., active smoking and, to a lesser degree, environmental exposures) [2, 7, 18, 44].

Smoking: Cigarette smoking is the most commonly identified correlate with both chronic bronchitis during life and extent of emphysema at postmortem. The prevalence of COPD shows a dose-response relationship with the number of pack-years of tobacco consumed. Some 90% of all COPD patients are current or former tobacco smokers. Experimental studies have shown that prolonged cigarette smoking impairs respiratory epithelial ciliary movement, inhibits function of alveolar macrophages, and leads to hypertrophy and hyperplasia of mucus-secreting glands; massive exposure in dogs can produce emphysematous changes. Cigarette smoke also inhibits antiproteases and causes polymorphonuclear leukocytes to release proteolytic enzymes acutely. Cigarette smoke can produce an acute increase in airways resistance due to vagally mediated smooth-muscle constriction by stimulating submucosal irritant receptors. Increased airways responsiveness is associated with more rapid progression in patients with chronic airways obstruction. Obstruction of small airways is the earliest demonstrable mechanical defect in young cigarette smokers and may disappear completely after cessation of smoking. Although smoking cessation does not result in complete reversal of more pronounced obstruction, there is a significant slowing of the decline in lung function in all smokers who give up cigarettes. Passive exposure to tobacco smoke correlates with respiratory symptoms such as cough, wheeze, and sputum production. Not only is cigarette smoking the most common single factor leading to chronic airways obstruction, it also adds to the effects of every other contributory factor to be discussed below [18, 34, 45].

Air Pollution: The incidence and mortality rates of both chronic bronchitis and emphysema may be higher in heavily industrialized urban areas. Exacerbations of bronchitis are clearly related to periods of heavy pollution with sulfur dioxide (SO_2) and particulate matter. While nitrogen dioxide (NO_2) can produce small-airways obstruction (bronchiolitis) in experimental animals exposed to high concentrations, there are no data convincingly implicating NO_2, at even the highest pollutant levels, in the pathogenesis or worsening of airways obstruction in humans [4, 5, 18].

Occupation: Chronic bronchitis is more prevalent in workers who engage in occupations exposing them to either inorganic or organic dusts or to noxious gases. Epidemiologic surveys have succeeded in demonstrating an accelerated decline in lung function in many such workers - e.g., workers in plastics plants exposed to toluene di-isocyanate, and carding room workers in cotton mills - suggesting that their occupational exposure contributes to their future disability [9, 14, 18, 20].

Infection: Morbidity, mortality, and frequency of acute respiratory illnesses are higher in patients with chronic bronchitis. Many attempts have been made to relate these illnesses to infection with viruses,

mycoplasmas, and bacteria. However, only the rhinovirus is found more often during exacerbations; that is to say, pathogenic bacteria, mycoplasmas, and viruses other than rhinovirus are found just as often between as during exacerbations [18, 34, 44].

Epidemiologic studies, however, implicate acute respiratory illness as one of the major factors associated with the etiology as well as the progression of chronic airways obstruction. Cigarette smokers may either transitorily develop or worsen small-airways obstruction in association with even mild viral respiratory infections. There is also some evidence that severe viral pneumonia early in life may lead to chronic obstruction, predominantly in small airways [18, 44].

GENETIC CONSIDERATIONS OF COPD

Despite the strong etiologic association between smoking and COPD, only 15 to 20% of smokers lose FEV1 at a rate fast enough to manifest COPD. Epidemiologic evidence of familial clustering of COPD cases is strong and repeated, suggesting that susceptibility to the effects of tobacco smoke has genetic determinants. Twin studies show that even after controlling for active and passive smoking, FEV1correlated more closely in monozygotic than dizygotic twins and more than in other family members with a lesser percentage of shared genotype. In first-degree relatives of a cohort of COPD patients with normal a1AT levels, FEV1 was reduced compared to controls but only among current or ex-smokers. Smoking and nonsmoking relatives of control subjects both had normal FEV1. These data suggest genetic risk factors that are expressed in response to smoking. a 1Antitrypsin Deficiency Thus far, deficiency of a1AT is the only genetic abnormality that has been specifically linked to COPD. a1AT is a 394-amino acid serine proteinase inhibitor whose synthesis is governed by a 12.2-kB 7-exon gene located at 14q32.1. a1AT synthesis is expressed primarily in the liver and to a lesser degree in neutrophils and monocytes. Hepatica1AT escapes into the general circulation, where it counteracts neutrophil elastase. Normal levels ofa1AT are 20 to 48 umol/L; levels above 11 umol/L (35% of normal) are considered protective. There are 75 known alleles ofa1AT, which are inherited in an autosomal codominant manner and are generally classified as normal (MM), deficient, null, or dysfunctional. The most common deficient allele, termed ZZ (or PiZZ phenotype), results from a single amino acid substitution 342Glu® Lys, which causes spontaneous polymerization of the polypeptide, markedly impeding its release into the circulation from the liver. What does escape is vulnerable to oxidation and spontaneous polymerization, further impeding its function. The retained material is associated with hepatic cirrhosis, while diminished circulating levels (2.5 to 7 umol/L, averaging 16% of normal) lead to antiprotease deficiency. PiZZ, the most common disease-relateda1AT abnormality, occurs in 1:2000 to 1:7000 persons of European descent and is rare in those of Oriental and African lineage. PiSS phenotypes are associated witha1AT levels of 15 to 33 umol (mean 52% of normal). Pinullhave no detectable antiprotease levels. Heterozygotes have intermediate levels of antiprotease. Clinically significant deficiency ofa1AT, with levels below 11 umol/L, has been associated with homozygous PiZZ, Pinullnull, or PinullZand the premature development of severe emphysema, chronic bronchitis, or bronchiectasis.a1AT deficiency accounts for 2% of observed cases of emphysema. Rare below age 25, the disease usually presents as dyspnea and cough in patients in their fourth decade. Although not a true population-based study, a large national registry of 1129 severea1 AT-deficiency cases indicated that the typical patient was in the mid-forties, with an FEV1 and a pulmonary diffusing capacity at or below 50% of the predicted levels. Most had exertional dyspnea and wheezing, but fewer than half reported a chronic cough. Nearly 80% had a positive family history of lung disease, and 25% reported a positive family history for liver disease. The average rate of decline of FEV1 is reported to be 100 to 130 mL per year for smokers and 50 to 80 mL per year for ex-smokers or lifetime non-smokers with a1AT deficiency [2, 6, 18, 21].

Pathologically, pan-acinar emphysema predominates, and radiographically, changes are more marked in the lower lobes. It is becoming increasingly apparent that tobacco smoking is an extremely important cofactor for the development of disease ina1AT-deficient individuals. Only a few lifetime nonsmokers with PiZZ develop emphysema. Most never have symptoms, have a normal rate of decline of FEV1, and live a normal life span. Many cases are discovered only as a consequence of family screening of emphysema patients. Because the total number of PiZZ individuals is unknown, the risk of disease for smokers is difficult to ascertain accurately. The risk of disease is lower still for heterozygotes with one M or S allele. Smoking is again an important cofactor [6, 18, 27].

PATHOLOGY OF COPD

The pathologic changes of COPD involve large and small airways and the terminal respiratory unit. Airway narrowing is seen in large and small airways and is caused by changes in their normal constituents in response to persistent inflammation. The airway epithelium is characterized by squamous metaplasia, atrophy of ciliated cells, and hypertrophy of mucus glands. The remodeled epithelium actively produces cytokines that amplify and sustain the inflammatory process. The small airways are the major site of airflow limitation. Small airways show a variety of lesions narrowing their lumina, including goblet cell hyperplasia, mucosal and sub-mucosal inflammatory cells, edema, peribronchial fibrosis, intraluminal mucus plugs, and increased smooth muscle. CD8+ T lymphocytes and B lymphocytes characterize the inflammatory infiltrate. The marked thickening of the subepithelial lamina reticularis, characteristic of asthma, is absent in COPD. In the central airways, sub-epithelial inflammation is present with increased numbers of eosinophils and CD8+ T lymphocytes. Unlike asthma, the eosinophils are not activated and do not de-granulate. Neutrophils are present in the epithelium but not in the subepithelial layers. In larger cartilaginous airways, chronic bronchitis is associated with hypertrophy of sub-mucosal mucus-producing glands. Quantitation of this anatomic change, known as the Reid index, is based on the ratio of the thickness of the sub-mucosal glands to that of the bronchial wall. In persons without a history of chronic bronchitis, the mean ratio is 0.44 ± 0.09, whereas in those with such a history, the mean ratio is 0.52 ± 0.08. Although a low index is rarely associated with symptoms and a high index is commonly associated with symptoms during life, there is a great deal of overlap. Therefore, many persons will have morphologic changes in large airways without having had chronic bronchitis. Emphysema begins as an increase in the number and size of alveolar fenestrae and results in the eventual destruction of alveolar septae and their attachments to terminal and respiratory bronchioles. Emphysema is classified according to the pattern of involvement of the gas-exchanging units (acini) of the lung distal to the terminal bronchiole. With centri-acinar emphysema, the distention and destruction are mainly limited to the respiratory bronchioles with relatively less change peripherally in the acinus. Because of the large functional reserve in the lung, many units must be involved in order for overall dysfunction to be detectable. The centrally destroyed regions of the acinus have a high ventilation/perfusion ratio because the capillaries are missing, yet ventilation continues. This results in a deficit of perfusion relative to ventilation, while the peripheral portions of the acinus have crowded and small alveoli with intact, perfused capillaries giving a low ventilation/perfusion ratio. This results in a deficit of ventilation relative to blood flow, giving a high alveolar-arterial PO2 difference (PAO2-PaO2). During normal aging, airspaces enlarge and alveolar ducts increase in diameter. These changes are extremely common in lungs from persons over age 50 and may be misidentified as emphysema. Pan-acinar emphysema involves both the central and peripheral portions of the acinus, which results, if the process is extensive, in a reduction of the alveolar-capillary gas exchange surface and loss of elastic recoil properties. When emphysema is severe, it may be difficult to distinguish between the two types, which most often coexist in the same lung [2, 18, 29].

PATHOPHYSIOLOGY OF COPD

Airflow Limitation: Although both chronic bronchitis and emphysema can exist without evidence of obstruction, by the time a patient begins to experience dyspnea as a result of these processes, obstruction is always demonstrable. Airflow limitation and increased airways resistance may be caused by loss of elastic recoil driving passive exhalation due to emphysema, by increased collapsibility of small airways through loss of radial traction on airways, or to increased resistance due to intrinsic narrowing of small airways. In addition to providing radial support to airways during quiet breathing, the elastic recoil properties of the lung serve as a major determinant of maximal expiratory flow rates. The static recoil pressure of the lung is the difference between alveolar and intra-pleural pressure [18, 29]. During forced exhalations, when alveolar and intra-pleural pressures are high, there are points in the airway at which bronchial pressure equals pleural pressure. Flow does not increase with higher pleural pressure after these points become fixed, so that the effective driving pressure between alveoli and such points is the elastic recoil pressure of the lung. Hence maximal expiratory flow rates represent a complex and dynamic interplay among airways caliber, elastic recoil pressures, and collapsibility of airways. Correlative studies of structure and function suggest that small-airway narrowing is the most important correlate of airflow obstruction, followed by loss of elastic recoil. Collapsibility is probably a less important factor. As a direct consequence of the altered pressure-airflow relationships, the work of breathing is increased in bronchitis and emphysema. Since flow-resistive work is flow rate-dependent, there is a disproportionate increase in the work of breathing when ventilation must be increased, as in exercise [10, 18, 25].

Hyperinflation: The residual volume and functional residual capacity (FRC) are almost always higher than normal. Since the normal FRC is the volume at which the inward recoil of the lung is balanced by the outward recoil of the chest wall, loss of elastic recoil of the lung results in a higher FRC. In addition, prolongation of expiration in association with obstruction would lead to a dynamic increase in FRC (dynamic hyperinflation) if inspiration is initiated before the respiratory system reaches its static balance point. Dynamic hyperinflation contributes additionally to the discomfort associated with airflow obstruction by flattening the diaphragm and placing it at a mechanical disadvantage due to shortened diaphragmatic fiber length and a perpendicular insertion with the lower ribs. The exertional increase in end-expiratory lung volume and consequent decrease in inspiratory capacity have been strongly associated with the degree of dyspnea. Elevations of total lung capacity (TLC) are frequent. The exact cause is uncertain, but increases in total lung capacity are often found in association with decreases in the elastic recoil of the lung. Although the vital capacity is frequently reduced, significant airways obstruction can be present with a normal to near-normal vital capacity [10, 18, 25, 37].

Impaired Gas: Exchange Mal-distribution of inspired gas and blood flow is always present to some extent. When the mismatching is severe, impairment of gas exchange is reflected in abnormalities of arterial blood gases. Small-airway narrowing causes a decrease in ventilation of their distal alveolar acini. When alveolar capillaries remain intact, this results in mismatching of ventilation and blood flow, reduced ventilation-perfusion ratios, and mild to moderate hypoxemia. With emphysema, destruction of alveolar walls may decrease alveolar capillary perfusion as well, better preserving ventilation-perfusion matching, and PaO2. Shunt hypoxemia is unusual [18, 27].

There are regions of the lung with a deficit of perfusion in relation to ventilation that increase the wasted ventilation ratio (i.e., Vd/Vt). At a normal resting CO2 production, the net effective alveolar ventilation, as reflected by the arterial PCO2, may be excessive, normal, or insufficient, depending on the relationship of the overall minute volume to the wasted ventilation ratio. The severity of gas exchange disturbances and, in large part, the clinical manifestations depend on the ventilatory response to the disordered lung function. Some patients, at the cost of extremely high effort of breathing and chronic

dyspnea, maintain a strikingly increased minute volume, which results both in a normal to low arterial PCO2, despite the high Vd/Vt, and a relatively high arterial PO2, despite the high difference, PAO2-PaO2. Other patients with only modest increases in effort of breathing and less dyspnea maintain a normal to only moderately elevated minute volume at the cost of accepting a high arterial PCO2 and a severely depressed arterial PO2. Factors that account for clear differences in ventilatory responses among patients have been studied and debated for years. The bulk of available evidence suggests that those patients who maintain relatively normal or low arterial PCO2 levels are those with an increased ventilatory drive relative to their blood gas values, and those who chronically maintain high arterial PCO2 and lower PO2levels have a diminished ventilatory drive in relation to their more severely deranged blood gas values. It is not at all certain whether individual differences are accounted for by variations in peripheral or central chemoreceptor sensitivity or through other afferent pathways [18, 37, 44].

Pulmonary Circulation: The pulmonary circulation malfunctions not only in terms of regional distribution of blood flow but also in terms of abnormal overall pressure-flow relationships. In advanced disease, there is often mild to severe pulmonary hypertension at rest, with further increases disproportionate to cardiac output elevations during exercise [18, 41].

A reduction in the total cross-sectional area of the pulmonary vascular bed can be attributed to thickening of medium and large muscular pulmonary arteries, to enhanced contraction of vascular smooth muscle in pulmonary arteries and arterioles, as well as to destruction of alveolar septa with loss of capillaries. Rarely does loss of capillaries alone lead to severe pulmonary hypertension with Cor pulmonale, except as a near-terminal event [18, 41, 44].

Of more importance is the constriction of pulmonary vessels in response to alveolar hypoxia. The pulmonary arteries of patients with severe hypoxemia COPD have been shown to exhibit increased contractility and impaired relaxation in response to pharmacologic stimuli in vitro. These differences between the pulmonary arteries of COPD patients and normal individuals are abolished by inhibition of NO synthase, suggesting that patients develop an endothelial defect in NO synthesis. The constriction is somewhat reversible by an increase in alveolar PO2 with therapy. There is a synergism between hypoxia and acidosis that assumes importance during episodes of acute or chronic respiratory insufficiency. Chronic hypoxia, especially in concert with carboxyhemoglobinemia, often seen with heavy cigarette smoking, leads not only to pulmonary vascular constriction but also to secondary erythrocytosis. The latter, although not proved to be a significant contributor to pulmonary hypertension, could add to pulmonary vascular resistance. Chronic afterload on the right ventricle leads to hypertrophy and, in association with disordered blood gases, ultimately to failure. Hypoventilation may occur during rapid eye movement sleep and lead to desaturation, which may be severe. Repeated desaturation may cause pulmonary hypertension [18, 41, 13, 30].

Renal and Hormonal Dysfunction: Chronic hypoxemia and hypercapnia have been shown to cause increased circulating levels of norepinephrine, renin, and aldosterone and decreased levels of antidiuretic hormone. Renal arterial endothelium in COPD patients exhibits defects similar to those seen in the pulmonary arteries, shifting renal blood flow from the cortex to the medulla and impairing renal functional reserve. The combination of hemodynamic and hormonal disturbances leads to defective excretion of salt and water loads and, together with right ventricular dysfunction, to the plethoric and cyanotic manifestations of some patients with COPD [18, 25].

Cachexia: Weight loss sometimes occurs in patients with advanced COPD. A body-mass index (BMI) < 25 kg/m2 is associated with increased frequency of exacerbations and with significantly reduced survival. Cachexia has been attributed to caloric intake failing to keep pace with energy expenditures

associated with increased work of breathing, but more recent evidence suggests that a biochemical basis is more likely. Hypoxemia leads to increased circulating levels of tumor necrosis factor a (TNF-a), and weight loss has now been correlated with levels of the latter [18, 35, 38].

Peripheral Muscle Dysfunction: Protein and muscle are lost as part of wasting in advanced COPD. Skeletal muscle bulk is lost with proportional reductions in strength. Proximal limb girdle muscles of the upper and lower extremities are particularly affected, contributing to dyspnea with activities of daily living. Fiber composition in skeletal muscle changes, favoring endurance over strength. These changes occur in parallel with FEV1and independently of glucocorticoid use, which can also cause myopathy and muscle weakness [18, 31, 44].

Osteoporosis: Loss of bone density is common in advanced disease. Over half of COPD patients lose more than 1 SD of bony density, and more than one-third have values more than 2 SDs below normal. Vertebral fractures are especially common. These changes are even more severe in patients receiving chronic glucocorticoid therapy [18, 43].

NATURAL HISTORY OF COPD

COPD is identified by the presence of an abnormal FEV1 in middle age, usually early in the fifth decade, and is characterized by an accelerated decline of FEV1 with aging. In normal individuals, FEV1 normally reaches a lifetime peak at age 25 and undergoes a linear decline of about 35 mL per year thereafter. Annual loss of FEV1 among susceptible individuals who develop COPD is between 50 and 100 mL per year [10, 18].

Greater rates of decline have been associated with mucus hypersecretion, especially in men, and with bronchial hyper-reactivity. Acute exacerbations do not alter the rate of decline. Dyspnea and impairment of physical work capacity are characteristic only of moderately severe to severe airways obstruction. There is considerable variation among individual patients [10, 18].

The majority of patients usually experience exertional dyspnea when FEV1falls below 40% of predicted and have dyspnea at rest when the FEV1less than 25% of predicted. In addition to dyspnea at rest, CO2 retention and Cor pulmonale frequently occur when the FEV1falls to 25% of predicted. With a respiratory infection, small changes in the degree of obstruction can make a large difference in symptoms and gas exchange. Thus small therapeutic gains may have rewarding results [10, 18, 35].

CLINICAL MANIFESTATIONS OF COPD

History: Patients with COPD are most often tobacco smokers with a history of at least one pack per day for at least 20 years. The disease is only rarely seen in nonsmokers. Onset is typically in the fifth decade and often comes to attention as a productive cough or acute chest illness. Exertional dyspnea is usually not encountered until the sixth or seventh decade. The patient's perception of dyspnea correlates poorly with physiologic measurements, especially among older patients [18]. A morning "smoker's cough" is frequent, usually mucoid in character but becoming purulent during exacerbations, which in early disease are intermittent and infrequent. Volume is generally small. Production of more than 60 mL/d should prompt investigation for bronchiectasis. The frequency and severity of cough generally do not correlate with the degree of functional impairment. Wheezing may be present but does not indicate severity of illness. As COPD progresses, exacerbations become more severe and more frequent. Gas exchange disturbances, worsen and dyspnea becomes progressive. Exercise tolerance becomes progressively limited. With worsening hypoxemia, erythrocytosis and cyanosis may occur. The development of morning headache may indicate the onset of significant CO2 retention. In advanced disease, weight loss is frequent and correlates with an adverse prognosis. When blood gas derangements are severe, Cor pulmonale may manifest itself by

peripheral edema and water retention. Anxiety, depression, and sleep disturbances are not infrequent [2, 18, 33].

Physical Findings: The physical examination has poor sensitivity and variable reproducibility in COPD. Findings may be minimal or even normal in mild disease, requiring objective laboratory data for confirmation. In early disease, the only abnormal findings may be wheezes on forced expiration and a forced expiratory time prolonged beyond 6 s. With progressive disease, findings of hyperinflation become more apparent. These include an increased antero-posterior diameter of the chest, inspiratory retraction of the lower rib margins (Hoover's sign), decreased cardiac dullness, and distant heart and breath sounds [18]. Coarse inspiratory crackles and rhonchi may be heard, especially at the bases. To gain better mechanical advantage for their compromised respiratory muscles, patients with severe airflow obstruction may adopt a characteristic tripod sitting posture with the neck angled forward and the upper torso supported on the elbows and arms. Breathing through pursed lips prolongs expiratory time and may help reduce dynamic hyperinflation. Cor pulmonale and right heart failure may be evidenced by dependent edema and an enlarged, tender liver. With pulmonary hypertension, a loud pulmonic component of the second heart sound may be audible, along with a right ventricular heave and a murmur of tricuspid regurgitation; these findings may be obscured by hyperinflation. If right-sided pressures are sufficiently high, neck veins may elevate instead of collapse with inspiration (Kussmaul's sign). Cyanosis is a somewhat unreliable manifestation of severe hypoxemia and is seen when severe hypoxemia and erythrocytosis are present [2, 7, 18, 21].

Radiographic Findings: A postero-anterior and lateral chest film should be obtained primarily to exclude competing diagnoses. They may be entirely normal in mild disease. As COPD progresses, abnormalities reflect emphysema, hyperinflation, and pulmonary hypertension. Emphysema is manifested by an increased lucency of the lungs. In smokers, these changes are more prominent in the upper lobes, while in a1AT deficiency, they are more likely in basal zones. Local radiolucencies >1 cm in diameter and surrounded by hairline arcuate shadows indicate the presence of bullae and are highly specific for emphysema [18]. With hyperinflation, the chest becomes vertically elongated with low flattened diaphragms. The heart shadow is also vertical and narrow. The retrosternal airspace is increased on the lateral view, and the sternal-diaphragmatic angle exceeds 90°. In the presence of pulmonary hypertension, the pulmonary arteries become enlarged and taper rapidly. The right heart border may become prominent and impinge on the retrosternal airspace. The presence of "dirty lung fields" may reflect the presence of bronchiolitis. Computed tomography has greater sensitivity and specificity for emphysema than the plain film but is rarely necessary except for the diagnosis of bronchiectasis and evaluation of bullous disease. Non-homogeneous distribution of emphysema is thought by some to be an indicator of suitability for lung volume reduction surgery (LVRS) [18, 43, 44].

PULMONARY FUNCTION TESTING

Because of the imprecision of clinical findings, objective evaluation of the presence, severity, and reversibility of airflow obstruction is essential in the diagnostic evaluation of COPD. A normal FEV1 essentially excludes the diagnosis. The spirogram in COPD shows decreased volume changes with time and a failure to reach a plateau after 3 to 5 s. continued airflow may be evident for 10 s or more on forced exhalation. The flow-volume curve shows diminished expiratory flow at all lung volumes [18, 43]. Expiratory flow is concave to the volume axis. When flow is plotted against absolute lung volume, the entire curve is shifted to higher volumes, reflecting hyperinflation. Serial spirometry is important in assessing the rate of decline of FEV1. Reversibility is assessed by spirometry before and after administration of an inhaled bronchodilator, most often a short-actingb2-adrenergic agonist. Testing should be performed when the patient is clinically stable. Short-acting bronchodilators should be withheld for 6 h, long-acting dilators for

12 h, and theophylline for 24 h prior to testing. A significant response is an increase of at least 12% and 200 mL in either FEV1or forced vital capacity (FVC). Post bronchodilator FEV1 is useful for prognostication. Although only one-third of COPD patients show a significant response to an inhaled bronchodilator in the pulmonary function laboratory on any one day, two-thirds will show a significant response when tested with different bronchodilators on several different occasions. The degree of bronchodilator response at any one testing session does not predict the degree of clinical benefit to the patient. Therefore, bronchodilators are given irrespective of the acute response obtained in the pulmonary function laboratory. The American Thoracic Society recommends staging COPD by FEV1. Stage I, mild disease, is defined as FEV1 50% predicted; stage II, moderate disease, 35 to 49% predicted; and stage III, severe disease [5,18, 43].

TREATMENT OF COPD

Treatment of COPD is based on the principles of prevention of further evolution of disease, preservation of airflow, preservation and enhancement of functional capacity, management of physiologic complications, and avoidance of exacerbations. Smoking Cessation [18, 38, 43].

The Lung Health Study has demonstrated that elimination of tobacco smoking confers significant survival benefit to patients with COPD. Prolonged survival is associated with reduced rates of malignancy and cardiovascular disease as well as with a significant increment inFEV1in the first year after smoking cessation. The rate of decline of FEV1reverts back to that of a nonsmoker. Although bronchodilator therapy produces similar first-year gains in FEV1, pharmacotherapy alone does not modify the decline of airflow over time. Even unsuccessful quitters show significant benefits when compared to continuing smokers. Despite the demonstrated benefits of smoking cessation, sustained quitting is difficult to achieve. Overall, only 6% of smokers succeed in quitting long term, and 70 to 80% of short-term quitters start smoking again. Successful quitting requires concerted active and continuing intervention by the physician [18, 38, 43].

The physician should address the issue in regular patient visits, assess the patient's readiness to quit, advise the patient as to the best methods for smoking cessation, provide emotional and pharmacologic support, and arrange close follow-up of the patient's efforts. The concept of "lung age" may be helpful in promoting smoking cessation by determining the age at which the observed FEV1would be a normal finding. Lungs of 50- to 60-year-old smokers may be "normal" for a 70- to 80-year-old individual. Nicotine patches and nicotine polacrilex gum improve quit rates, especially among nicotine-dependent smokers. The addition of oral bupropion at 150 mg twice daily produces significant additional benefit, with a 1-year sustained abstinence rate of 22.5% compared to 6% for placebo. Smoking cessation is typically associated with weight gain of 3 to 4 kg. To minimize weight gain, reluctance to quit, and relapse, prospective quitters should be counseled to reduce caloric intake and to increase physical activity [18, 38, 43, 44].

Bronchodilators: These drugs improve dyspnea and exercise tolerance by improving airflow and by reducing end-expiratory lung volume and air-trapping. Although airflow limitation is relatively fixed, some degree of response to bronchodilator medication is usually present. Bronchodilator medication is available in metered-dose inhaler (and some dry-powder inhalers) and in nebulizable and oral forms. Inhalers deliver medications directly to the airways and have limited systemic absorption and side effects. Proper use requires timing and coordination of inspiration and inhaler actuation and presents frequent difficulties for chronic lung patients. These problems can usually be overcome with education and with the use of holding chambers. Aerosol nebulizers have no pharmacologic advantage over metered-dose inhalers. Their use should be limited to patients who remain unable to master metered dose inhalers adequately. Oral medication is associated with higher rates of adherence than inhalers but shows higher rates of systemic side effects without superior bronchodilation. Three major classes of bronchodilators are commonly employed in the treatment of patients with COPD: short- and long-actingb2-adrenergic agonists, anticholinergics, and

theophylline derivatives. Short-acting b2-agonists (albuterol, pirbuterol, terbutaline, metaproterenol) are relatively bronchoselective with minimal effects on heart rate and blood pressure. They produce significant bronchodilation at 5 to 15 min and remain effective for 4 to 6 h. Long-acting b2-agonists (oral sustained-release albuterol and inhaled salmeterol) have an onset of action of 15 to 30 min and a 12-h duration of action. Anticholinergic agents (ipratropium bromide) have a 30- to 60-min onset of action and a 4- to 6-h duration. Theophyllines are generally administered orally in 12- or 24-h preparations. Regular use of ipratropium may lead to improvements in baseline FEV1when compared with short-acting b2-agonists. When used together, ipratropium and short-actingb2-agents show greater clinical efficacy than either agent alone, without an increase in side effects. Salmeterol as a single agent produces longer lasting bronchodilation than ipratropium, improves baseline FEV1over time, and is not associated with loss of efficacy over a period of several months. Salmeterol, however, has not yet been evaluated as a component of combination therapy. Theophylline is a weak bronchodilator with a narrow therapeutic window. Much of its clinical benefit derives from effects other than bronchodilation; therapeutic doses of theophylline increase ventilatory drive, enhance diaphragmatic contractility, and increase cardiac output. About 20% of COPD patients respond to theophylline with improved airflow, exercise tolerance, and quality of life. Theophylline produces additional benefits in exercise capacity and quality of life when used in combination with short-actingb2-adrenergic agonists. The therapeutic range for theophylline is commonly given as 10 to 20 ug/mL, with greater efficacy but greater toxicity seen at higher serum levels. The risk of toxicity is greater in older patients and in those with heart and kidney disease. Optimal dosing must balance the competing considerations of risk and benefit for each individual patient [13,18, 43].

Glucocorticoids: Because COPD, like asthma, is a disease associated with airway inflammation, glucocorticoids are an intuitively attractive therapeutic modality. Nevertheless, results of clinical trials of glucocorticoid therapy in COPD patients have shown less impressive benefits when compared to patients with asthma. The degree of response to glucocorticoids appears to correlate with the presence of asthmatic features, but data supporting their use is limited. Only 10% more patients show subjective benefit and increase their FEV1or forced vital capacity by at least 20% when compared to those on placebo. Responders cannot be reliably identified on clinical grounds, although response to an inhaled b2-agonist is commonly used as a predictor. The benefits of a 10- to 14-day trial of 30 to 40 mg/d of prednisone for patients with stage III disease who have not responded adequately to mixed bronchodilator therapy remain to be proven. Long-term systemic glucocorticoid use is associated with multiple side effects. In particular, they have been associated with worsened osteoporosis and increased risk of vertebral fracture. If systemic steroids are used, the lowest effective dose should be employed and alternate-day dosing used whenever possible. The use of inhaled glucocorticoids ameliorates systemic side effects. Three large clinical trials have shown that inhaled glucocorticoids do not alter the rate of decline of FEV1. While an inhaled glucocorticoid does not decrease the number or frequency of COPD exacerbations, it may decrease their severity and reduce the need for hospitalization. Symptoms and exercise tolerance improve on inhaled glucocorticoids [13, 18, 43].

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