Chronic Obstructive Pulmonary Disease: Focus on Early Diagnosis

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Practitioners usually diagnose COPD when it is advanced, too late to reduce morbidity and mortality. These authors offer a blueprint for making the diagnosis at an early stage of the disease, when intervention can make a difference.

The number of deaths in the United States from chronic obstructive pulmonary disease (COPD) has nearly doubled in the last 30 years, making this disease the fourth leading cause of death.[1] Because the number of deaths will continue to increase, COPD is expected to become the third leading cause of death by 2020.[2] About 6% of the U.S. population has been given a diagnosis of COPD by a physician.[3,4] Even though this proportion is alarmingly high, it is thought to represent only half of those with evidence of impaired lung function due to COPD.[5]

The burden of COPD on society and on the health care system is likewise staggering. Patients with COPD utilize health care far more than those without the disease. On average, COPD patients make more frequent office visits than the population overall, and an estimated 1.6 million hospitalizations are related to COPD.[6] The estimated direct cost of medical care is $20 billion and the estimated indirect cost of lost productivity is $16 billion.[7] Though the health care burden COPD causes should command more attention from the medical community, the condition is surprisingly neglected. The reasons for this neglect relate to shifting definitions of what constitutes the disease, its variety of presentations, and underutilization of spirometry.

Because smoking, the chief risk factor for COPD, is more prevalent among veterans than the general public, reducing the morbidity and mortality from COPD is an especially important challenge for VA practitioners. Achieving this goal requires being able to diagnose COPD in its early stages, which can lead to the prompt interventions that can slow the disease's progress. Early diagnosis is not an easy task; however, because many patients have only vague symptoms and normal examinations early in the disease course. The key lies in knowing who is at risk, identifying possible signs and symptoms, and using spirometry to confirm clinical suspicion.

CHANGING DEFINITIONS

COPD has been defined in many ways over the years. Until recently, it was an umbrella term that encompassed chronic bronchitis and emphysema. Chronic bronchitis was a clinical diagnosis based on presence of a productive cough for 3 months in 2 consecutive years. Emphysema, on the other hand, was a pathologic diagnosis based on the presence of abnormal permanent enlargement of air spaces. The illnesses of individual patients represent a spectrum between these 2 entities—leading to the realization that COPD may have many "phenotypes," each with a differing clinical course and response to treatment.[8]

To decrease confusion, a combined initiative of the World Health Organization and National Heart, Lung, and Blood Institute resulted in the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[5] This consortium offered a new unifying definition of COPD:

> "…preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."

Beyond simplifying the definition of COPD to the presence of airflow obstruction, this disease description also attempts to dispel some of the nihilism historically associated with the diagnosis. Notably, it highlights the preventable and treatable nature of this disease. The description also draws attention to the extrapulmonary manifestations of COPD that only now are being fully recognized.[9]

These extrapulmonary manifestations, which include cardiovascular

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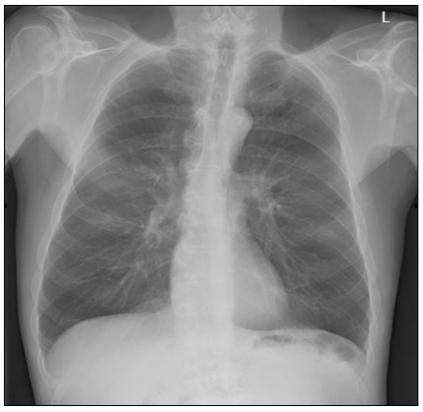

Figure 1. Chest roentegenogram of typical patient with COPD demonstrating hyperinflated lungs and flattened diaphragms. COPD = chronic obstructive pulmonary disease.

disease, osteoporosis, and muscle wasting, are thought to be the result of systemic inflammation that is induced by inflammation present in the lung (see "COPD—Not Just a Lung Disease" on page 24). This association has been demonstrated by the increased levels of inflammatory markers in patients with COPD, including C-reactive protein, tumor necrosis factor–alpha, and various cytokines.[10] The exact source of the systemic inflammation has not yet been elucidated but may simply be induced by inflammatory mediators present in the lung.[9]

WHO IS AT RISK FOR COPD?

According to the GOLD consortium, COPD represents an "abnormal inflammatory response of the lung to noxious particles or gases."[5] Those prone to COPD development are believed to have a genetic predisposition that results in an amplified response to stimuli.[11] Tobacco use is the primary risk factor for development of COPD, with cigarette smokers at higher risk than pipe or cigar smokers.[12] But passive smoking or secondhand smoke exposure must not be underestimated, as this exposure also has been shown to increase the risk for developing COPD.[13]

Tobacco use is not the only risk factor for COPD, however. Occupational exposure to dust, fumes, or smoke also can result in an inflammatory response that can lead to development of COPD. The American Thoracic Society concluded that occupational dust and fume exposure might play a role in 10% to 20% of patients presenting with COPD.[14] Globally, indoor air pollution resulting from biomass fuel use for cooking and heating is another significant cause of COPD.[15] Surprisingly, the significance of outdoor air pollution in major urban centers in the development of COPD has not been conclusively demonstrated.[5]

CLINICAL PRESENTATION OF COPD

Most patients with COPD receive a diagnosis in the later stages of the disease when they have already lost 50% or more of their lung function.[16] As the disease progresses, their symptoms become more classic and diagnosis more apparent. The typical presentation is a chronic cough, occasionally productive, with progressive dyspnea.[5] The patient may have a history of recurrent episodes of bronchitis, often treated with repeated courses of antibiotics. On examination, he or she often will have prolonged expiration with possible wheezing. Findings in advanced disease include accessory muscle use, pursed lip breathing, barrel chest, peripheral cyanosis, and edema. The patient with end-stage disease has reduced muscle mass and a low body mass index (BMI). Typical chest roentgenogram (CXR) findings include hyperinflation and a flattened diaphragm (Figure 1). Two phenotypes that are classic for end-stage COPD are the "pink puffer" (primary diagnosis of emphysema marked by increased respiratory rate causing hyperventilation and skin redness) or "blue bloater" (primary diagnosis of

Spirometry: An Underused Technology

Despite being a safe and inexpensive study, spirometry is underutilized. A recent study showed that two-thirds of patients with the diagnosis of COPD discharged from hospitals never had spirometry.[1] The VA is not exempt from these omissions: According to a review of a VA database, the medical record of only 34% of veterans with the diagnosis of COPD had spirometric results.[2,3] And another recent review from the Boise VA showed that only a third of patients with suggestive clinical symptoms of COPD had spirometry to confirm the diagnosis.[4]

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Table 1. COPD – Population screener

During the past 4 weeks, how much of the time did you feel short of breath?	
None of the time	0 points
A little of the time	0 points
Some of the time	1 point
Most of the time	2 points
Do you ever cough up any "stuff," such as mucus or phlegm?	
No, never	0 points
Occasional colds	0 points
Few days a month	1 point
Most days a week	1 point
Yes, every day	2 points
Please select the answer that best describes you in the past 12 months. I do less than I used to because of my breathing problems.	
Strongly disagree	0 points
Disagree	0 points
Unsure	0 points
Agree	1 point
Strongly agree	2 points
Have you smoked at least 100 cigarettes in your entire life?	
No	0 points
Yes	2 points
How old are you?	
Aged 35–49 years	0 points
Aged 50–59 years	1 point
Aged 60–69 years	2 points
Aged 70+ years	2 points
Five points or higher increase likelihood of COPD	

Adapted from Martinez FJ et al. *COPD*. 2008;5(2):85–95 with permission from Informa Healthcare Communications.[18]

chronic bronchitis marked by cyanosis, right heart failure, and swelling of ankles and veins).

THE EARLY DIAGNOSIS

Identifying patients with mild disease is a clinical challenge. Consider these 3 patients:

- 60-year-old man with a productive cough and dyspnea on exertion
- 70-year-old woman with low energy and sedentary lifestyle
- 50-year-old man with yearly episodes of bronchitis

Despite their diverse presentations, all 3 of these patients may have COPD. Mild disease has been termed the silent phase of COPD as symptoms are minimal and the physical exam near normal.[17] Often, patients are unaware of their disease and disability, as they have unconsciously modified their lifestyles to fit within their respiratory capacity. They accept any symptoms as a natural part of aging and do not discuss them with their health care providers. They may report only nonspecific complaints, such as fatigue, limited activity tolerance, and a general malaise. The patient who avoids stairs because he is "too old" is a common scenario. Other patients may stop certain activities, such as bringing in groceries from the car, walking around the block, or vacuuming because the activity is too strenuous. These lifestyle changes should alert the health care provider to the possibility that the patient has COPD.

To elicit symptoms that patients may not recognize on a conscious level, directly questioning the patient with risk factors and vague symptoms is essential. Several screening tools are available to assist with this process. One such tool is the COPD-Population Screener questionnaire, available at www.copdscreener.com, which was developed by identifying 5 questions out of dozens that predict airway obstruction (Table 1).[18] A cutoff score of 5 or more targets patients likely to have COPD.

Spirometry or pulmonary function testing (spirometry, lung volumes, and diffusing capacity) to confirm the diagnosis and to stage the severity is the next step for any patient with risk factors and suggestive symptoms (see "Spirometry: An Underused Technology" on page 18). Advances in technology have allowed spirometry to be miniaturized

Table 2. Spirometric classification of COPD severity*

Stage	Severity	Value
Stage 1	Mild	$FEV_1 \geq 80\%$
Stage 2	Moderate	$FEV_1 \leq 50\%$ to $< 80\%$
Stage 3	Severe	$FEV_1 \leq 30\%$ to $< 50\%$
Stage 4	Very severe	$FEV_1 < 30\%$ or $FEV_1 < 50\%$ and $PaO_2 < 60$ mmHg

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity. *All with postbronchodilator $FEV_1/FVC < 0.7$. Adapted from Global Initiative for Chronic Obstructive Lung Disease.[5]

Table 3. Differential diagnosis of COPD

- Asthma
- Bronchiectasis
- Bronchiolitis
- Congestive heart failure
- Cystic fibrosis
- Interstitial lung disease
- Pneumoconiosis
- Sarcoidosis

COPD = chronic obstructive pulmonary disease.

and moved from specialty pulmonary labs to handheld devices that can be used in medical offices. Because of these advances, spirometry is widely available.

Simple spirometry measures the volume of air expired by the patient as a function of time. The volume of air forcefully expired in 1 second (FEV_1) over the total volume of air forcefully expired (forced vital capacity or FVC) gives the FEV_1/FVC ratio. The GOLD group defines COPD as a FEV_1/FVC of less than 0.70 measured after administration of a short-acting bronchodilator. The severity is defined by the percent of predicted FEV_1 (Table 2).[5]

Although the GOLD definition is simple, it does result in false positive results in older individuals as the FEV_1/FVC decreases with normal aging. The American Thoracic Society and European Respiratory Society, therefore, recommend using confidence intervals normalized to patients' demographics.[19] Even though an older patient has an FEV_1/FVC of less than 0.70, he may not necessarily be considered to have obstructive lung disease when this recommended adjustment is made.[20]

Full pulmonary function tests, which measure lung volumes and diffusing capacity, are not needed to identify obstruction, but they help to further characterize the severity of a patient's disease. Lung volume measurements aid in assessing severity of air trapping and hyperinflation, which occurs even in early disease and contributes to the breathlessness patients experience. In addition, patients with COPD often have a low diffusing capacity, commonly measured with the use of carbon monoxide. A low diffusing capacity usually represents emphysematous of the lung. Very low values (< 40% predicted) often presage the need for supplemental oxygen. Diffusing capacity is not used to determine the severity of emphysema in an individual patient, however.

Although many patients are given a COPD diagnosis on the basis of smoking history and respiratory complaints alone, a firm diagnosis, confirmed by spirometry, is crucial to properly assess disease severity as well as to institute appropriate therapy. Also, given that cough, phlegm, dyspnea, and wheezing are not specific for COPD, the differential diagnosis must be kept in mind even though the likely diagnosis is COPD (Table 3).

Occasionally, imaging that was not performed explicitly to identify COPD suggests the diagnosis. The CXR can demonstrate hyperinflation that is suggestive but not specific for COPD or the patient may have had computed tomography imaging of the chest that showed not only hyperinflation but emphysematous changes, bullous lung disease, and frank lung destruction. All these findings are highly suggestive of COPD, but demonstration of obstruction on spirometry is still required to confirm the diagnosis. Furthermore, these findings typically are noted in the later stages of COPD but also can be present in early-stage disease. Of course, absence of these findings should not be used as an indication that the patient does not have COPD.

INTERVENTIONS THAT WORK

By diagnosing COPD early, the practitioner can encourage the patient to engage in what is by far the most effective intervention in this disease: smoking cessation,[21] which significantly improves morbidity and mortality.[21,22] Indeed, the Lung Health Study showed that the accelerated annual decline of FEV_1 seen in smokers (70 mL/y to 100 mL/y) returns to the rate seen in nonsmokers (30 mL/y) with smoking cessation.[23,24] These findings mirror a landmark 1977 study of the natural history of COPD, which also demonstrated that not all smokers are susceptible to the effect of smoke on lung function (Figure 2).[25] The

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COPD—Not Just a Lung Disease

Recent studies have shown the role of systemic inflammation in many of the extrapulmonary manifestations of COPD; chief among these manifestations is weight loss. COPD patients, primarily in later stages of disease, also experience skeletal muscle atrophy, which further compromises their tolerance for exercise.[1] Scientists believe that various cytokines activate pathways can lead to muscle cell apoptosis.[2]

COPD also is a risk factor for heart disease, independent of smoking history. The systemic inflammation resulting from COPD is thought to contribute to plaque formation—itself an inflammatory process.[3,4] COPD also is believed to be a risk factor for osteoporosis beyond shared risk factors, such as age, steroid use, and nutrition status.[5] The list of diseases associated with COPD is increasing, making clear it is not simply a disease limited to the lungs. Fortunately, medications in development will attempt to address systemic manifestations of COPD.[6]

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younger patient has most to gain from smoking cessation, but even the elderly individual benefits. While smoking cessation does not reverse an already present reduction in lung function, it does slow the rate of decline to that of a nonsmoker of similar age. The reduction in decline in lung function translates into a delay in development of dyspnea, disability, and eventual death. In fact, early smoking cessation before the onset of dyspnea may delay symptoms until well into the seventh and eighth decade of life. Even the advanced dyspneic, disabled COPD patient may achieve several years of added life by giving up smoking.[26,27]

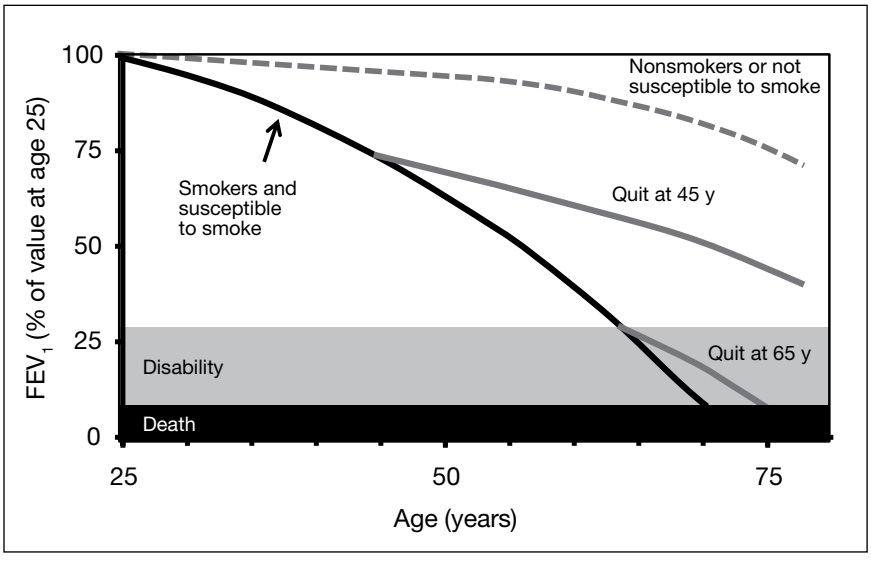

Figure 2. How smoking affects FEV_1, morbidity, and mortality in smokers compared with nonsmokers. Adapted from Fletcher C, Peto R. *BMJ*. 1977:1(6077):1645–1648 with permission from BMJ Publishing Group Ltd.[25] FEV_1 = forced expiratory volume in 1 second.

In contrast to smoking cessation, pharmacologic treatments often have been viewed as providing only symptomatic relief. But new data suggest that medication also may be able to alter disease trajectory. The medications that have showed greatest promise are the long-acting muscarinic antagonist, tiotropium, and the combination long-acting beta agonist, salmeterol, and the inhaled steroid, fluticasone. Secondary analysis of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study data suggested that tiotropium decreased the rate of decline in postbronchodilator FEV_1 in those younger than age 50 years.[28,29]

Table 4. BODE Index

Body mass index is scored as follows:
• Greater than 21 = 0 points
• Less than 21 = 1 point
FEV_1 (postbronchodilator percent predicted) is scored as follows:
• Greater than 65% = 0 points
• 50%–64% = 1 point
• 36%–49% = 2 points
• Less than 35% = 3 points
Modified Medical Research Council (MMRC) dyspnea scale is scored as follows:
• MMRC 0 = Dyspneic on strenuous exercise = 0 points
• MMRC 1 = Dyspneic on walking a slight hill = 0 points
• MMRC 2 = Dyspneic on walking level ground
o Must stop occasionally due to breathlessness = 1 point
• MMRC 3 = Dyspneic after walking 100 yd or a few minutes = 2 points
• MMRC 4 = Cannot leave house; dyspneic doing activities of daily living = 3 points
6-min walking distance is scored as follows:
• Greater than 350 m = 0 points
• 250 m–349 m = 1 point
• 150 m–249 m = 2 points
• Less than 149 m = 3 points

FEV_1 = forced expiratory volume in 1 second. Reprinted from Celli BR et al. *N Engl J Med*. 2004;350(10):1005–1012 with permission from Massachusetts Medical Society.[32]

Additionally, the Towards a Revolution in COPD Health (TORCH) study showed that the rate of decline in lung function decreased in the combination salmeterol/fluticasone group compared with patients given each medication individually.[30,31]

The efficacy of various medications is a fertile area for investigation that is beyond the scope of this review. A host of new pharmacologic agents are in development and will become available in the next decade. In addition, even those with advanced disease may benefit from some promising nonpharmacologic, nonsurgical treatment options, such as bronchoscopic lung volume reduction.

DETERMINING PATIENT PROGNOSIS

Various measures have been used to predict prognosis in COPD, including FEV_1, diffusing capacity for carbon monoxide, blood gas measurements, BMI, exercise capacity, clinical status, and radiographic measures of lung disease. A major advance was the development of the BODE index, which evaluates BMI, obstruction, dyspnea, and exercise tolerance (Table 4).[32] The success of this index is attributable to its combination of measures of both pulmonary and extrapulmonary manifestations of COPD. Compared with other measures, this index provides a better characterization of the different phenotypes of patients with COPD and allows for calculation of likely survival time. For example, the index can differentiate among patients who have the same FEV_1 but have markedly different symptoms and functional capacity and likely differing survival. This differentiation also may allow for identification of patient subgroups who would be good candidates for specific therapies or are at increased risk for complications—information that can be used to improve these patients' management.

THE FINAL WORD

Most patients with COPD already have severe disease when they are diagnosed.[16] This diagnostic delay is understandable because patients are most likely to consult their physicians when their symptoms have become significant and limiting. This also is the time when physicians are more apt to notice severe airflow limitation and possibly become aware of wheezing. In extreme but not uncommon instances, patients may present in respiratory failure with an acute exacerbation of COPD.

To make any meaningful attempt at preventing long-term morbidity and mortality from COPD, the disease must be diagnosed in its early stages when sufficient lung function remains to benefit from preventive interventions. The first step in diagnosis of early-stage COPD is to consider the diagnosis, keeping in mind that any patient with any tobacco use or dust/fume/smoke exposure is at risk.

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Clinical suspicion of COPD should be followed up with spirometry to confirm the diagnosis. This test is particularly invaluable in early disease when signs and symptoms are vague.

Early diagnosis of COPD encourages both patients and physicians to address the disease. The simple act of establishing a diagnosis can prompt the patient to make lifestyle changes, the most important of which is to stop smoking. Evaluating at-risk patients for COPD also reminds the practitioner of an important chronic disease that is easy to overlook in a busy office visit. ●

Author disclosures

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