

# Roger S. Mitchell Lecture

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## Chronic Obstructive Pulmonary Disease Phenotypes and Their Clinical Relevance

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Phenotype is defined as the outward physical manifestation of patients with chronic obstructive pulmonary disease (COPD); anything that is part of their observable structure, function, or behavior. As such, for patients with COPD, the time has come to move from a disease expressed solely by the degree of airflow limitation, to a much broader and resourceful characterization of COPD. Recent advances in the detection of specific clinical phenotypes, such as persistent hypoxemia, hyperinflation with inhomogeneous emphysema, frequent exacerbators, and patients with peripheral muscle dysfunction, are resulting in specific forms of approaches to include therapy that are affecting outcomes. Further, the investigation of the differential influence of gender on the development of COPD is finally catching our attention. In the area of basic science, we are beginning to understand different expressions of disease through genomics, proteomics, and metabolomics. Extensions of these findings and that of neglected aspects that may explain the clinical course of certain patients, such as their psychologic background, will certainly increase our understanding and provide more solid scientific rationale to the phenotypic characterization of patients with COPD. Further, such understanding will not only help explain the manifestations and course of the disease in particular patients but also help select for specific therapies. The hope is that, coupled with primary and secondary prevention, we can reverse the current epidemic and we can improve the well-being of patients affected by COPD.

Chronic obstructive pulmonary disease (COPD) has recently been redefined (1) as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences. From this definition, it follows that airflow limitation, best characterized by the FEV<sub>1</sub>, provides the underpinning of any phenotypic expression of the disease and that the presence of inflammation and systemic consequences are intrinsic important components of the disease that ought to be measured and characterized when describing patients with COPD.

The word “phenotype” needs to be defined. For this article, “phenotype” is defined as “the outward physical manifestation of patients with COPD; anything that is part of their observable structure, function, or behavior.” This provides a framework

upon which to group what we can document as particular characteristics of patients with COPD.

### AIRFLOW LIMITATION: THE DEFINING ELEMENT

The well-known work from Fletcher and coworkers (2) has dominated our way of defining the progression of COPD. Once people begin smoking, and if they are susceptible, their FEV<sub>1</sub> declines, and symptoms of breathlessness, cough, and phlegm develop. This landmark study helped develop the field because it provided clinicians and researchers with a practical framework to classify the disease and test interventions. Indeed, the spirometric staging of COPD has proved useful in predicting health status (3), use of health care resources (4), development of exacerbations (5, 6), and mortality (7). Unfortunately, the strict direct association between the rate of decline of FEV<sub>1</sub> and disease progression has placed undue constraints on different approaches to understand and to develop and test novel therapies. FEV<sub>1</sub> is a valued diagnostic tool, but it is hard to modify when, by definition, we exclude patients with reversibility (1, 8). Within the domain of airflow limitation, it was already evident that the presence of bronchial hyperreactivity conferred a phenotypic expression that was associated with worsened lung function. However, it has become increasingly clear that FEV<sub>1</sub> and its change do not fully represent the complex clinical manifestations of COPD (9, 10). The presence of emphysema and hyperinflation (11, 12), the increasingly important role of malnutrition (13), peripheral muscle dysfunction (14), and dyspnea (15) (the dominating symptom in COPD) reflect independent predictors of outcome. Finally, the sex and degree of comorbidity are defining phenotypic characteristics not described and poorly correlated with FEV<sub>1</sub>. This article summarizes the evidence and support for these phenotypes and their clinical implications. A representation of the currently accepted phenotypic expressions of COPD is shown in Figure 1.

### EMPHYSEMA AND HYPERINFLATION

Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis (1, 2). Therefore, a clinical “phenotype” for emphysema has to depend on methods other than pathology. First, it relies on the physiologic expressions of progressive emphysema. The loss of lung elastic recoil and development of expiratory flow limitation promote progressive air trapping with increase in the end-expiratory lung volume and decrease of the inspiratory capacity (IC). The static lung hyperinflation (LH) and its increase during exercise (dynamic hyperinflation) have been associated with limitations in the functional capacity of those patients (16, 17). Patients with emphysema also have decreased diffusion capacity, which is easily measured using the single-breath carbon monoxide (DL<sub>CO</sub>) method. In addition, the

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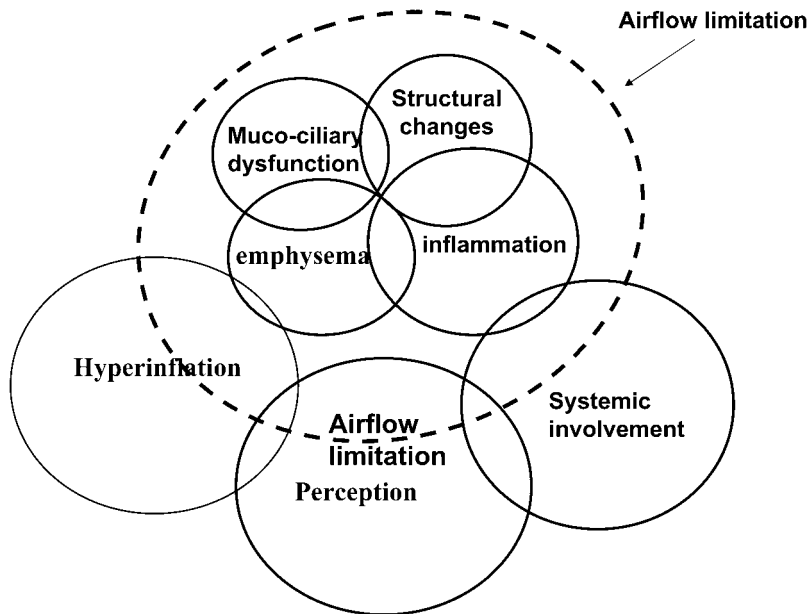
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**Figure 1.** Nonproportional Venn diagram summarizes some of the recognized pathophysiologic processes responsible for the airflow limitation (*discontinuous lines*) that defines chronic obstructive pulmonary disease. *Solid circles* represent phenotypic expressions of the disease that are related to outcomes. These phenotypic expressions, although related to airflow limitation, convey independent predictive information and are amenable to specific therapy.

advent of computed lung tomography (CT) with appropriate new analytic algorithms has provided the field with an excellent tool to investigate the severity, extension, and distribution of the lung destruction. An integration of physiologic data (low  $DL_{CO}$  and  $FEV_1$ ) with CT-generated information (homogenous distribution of emphysema) helped select individuals at high risk for death in the National Emphysema Therapy Trial (18). Furthermore, the use of CT and another physiologic test, the work capacity measured during a cardiopulmonary exercise test expressed in watts, was capable of selecting patients whose survival, exercise capacity, and health status improved after lung volume reduction surgery (11). In a recent publication, Casanova and coworkers (12) extended the observations relating hyperinflation to outcome. In a cohort of 629 patients, the IC/TLC ratio predicted respiratory and all-cause mortality better than  $FEV_1$ . It would be interesting to investigate the possible association between the inspiratory fraction or IC/TLC and the degree of emphysema as determined by CT scan to more objectively relate “emphysema” with “hyperinflation.” Independent of the degree of obstruction, the presence of hyperinflation, degree, and distribution of emphysema selects for a “phenotype” of patients for whom at least surgical and nonsurgical volume reduction seems to offer concrete therapeutic alternatives.

### SYSTEMIC INVOLVEMENT AND INFLAMMATION

It has been clearly established that some patients with COPD develop extrapulmonary manifestations (1), most of which are poorly related to the degree of airflow limitation. The earliest and best investigated is the development of important hypoxemia. Its presence was noted to confer a very poor prognosis, but, more importantly, its correction when lower than 55 mm Hg was associated with improved survival (19, 20). This observation is important as we look to the future because these landmark trials demonstrate that it is not necessary to alter the rate of decline of  $FEV_1$  to modify the natural course of the disease.

The observation that malnutrition as measured by the body mass index (BMI) was an independent predictor of death in patients with COPD (13), subsequently proven to be relatively frequent in less selected population and cohort studies (21), opened the gates to the possible presence of systemic conse-

quences of COPD through mechanisms that have yet to be fully explored. Whether the consequence of inflammation as suggested by the presence of elevated levels of serum tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) (22), imbalance in oxidants/antioxidants (23), increased work of breathing, or a combination of these mechanisms, low BMI ( $< 0.21$ ) is clearly a “phenotype” that needs to be recognized.

Similarly, it has long been recognized that most patients with COPD have limitation of their exercise capacity. Although the reason for this was originally thought to be impaired respiratory mechanics, the evidence supports the development of peripheral muscle dysfunction (24, 25), which may have an inflammatory basis (26). This topic, developed in more depth in subsequent chapters in this symposium, has important clinical implications. Poor exercise capacity, whether determined during a cardiopulmonary exercise test using the peak oxygen uptake (peak  $\dot{V}O_2$ ) (27) or by the simple timed walk test (28), is an excellent independent predictor of survival in these patients. It is possible that therapies aimed at preventing this problem, reversing it if present or even simple exercise training, could have profound impact on outcome.

Clinicians and researchers have associated the diagnosis of COPD with the progressive development of erythrocytosis and its consequences. Although this was perhaps the case in the past, recent evidence points to the frequent presence of anemia in 10 to 20% of patients with COPD (29). The cause of the anemia remains debatable. However, the evidence points to anemia of chronic diseases with its inflammatory nature. Furthermore, in the preliminary study recently reported by Cote and colleagues (29), the degree of anemia correlated with mortality independent of the degree of comorbidity.

The critical issue is whether the systemic manifestations of COPD could result from the “spillage” of inflammatory cytokines or activated cells, which then hone in on certain organs. In favor of this mechanism is the observation that levels of serum C-reactive protein, interleukin 6 (IL-6), leukotriene  $B_4$ , TNF- $\alpha$ , and other biomarkers are elevated in patients with COPD (30–33). If so, it may be possible to unravel these pathways and target specific molecules to prevent or reverse their pathogenic potential.

## SEX

Several recent studies have suggested sex differences in the diagnosis and clinical manifestations of COPD (34). Women are less responsive to long-term exercise therapy (35), score lower in quality-of-life questionnaires, manifest more reactive airways (36), and report more dyspnea for the same degree of airflow obstruction (35) than men. In a recent report, DeTorres and colleagues (37) showed that in patients attending a pulmonary clinic for COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stages II and III), women had smoked less, were younger, and had less comorbidity scores than men. For the same lung function, they had better oxygenation. However, women had more exacerbations, expressed more dyspnea, and had worse scores in all the domains of the quality-of-life questionnaires. These results indicate that more attention must be devoted to the characterization of the way in which exposure to inhaled particles (from cigarette or from biomass fuels) affect women.

## EXACERBATION FREQUENCY

The cost of COPD is staggering, reaching \$31.9 billion annually in the United States alone. Most of this is due to recurrent acute exacerbations that lead to emergency visits and hospitalizations. During an exacerbation, patients with COPD present to the clinician with worsened dyspnea, cough, phlegm production, or change in the color of previously produced phlegm, which may result in respiratory failure. After episodes of acute exacerbation, the patients report substantially decreased scores in their perception of health status (38) and, if admitted with respiratory failure, mortality at 1 yr can be as high as 50%. Several reports from the East London cohort (39, 40) have indicated that patients with similar degree of airflow limitation, caused by bacteria, viruses, or environmental factors, may have different rates of exacerbations, with a minority of the patients presenting with more than two exacerbations per year (frequent exacerbators). Not only do these patients score worse in health status questionnaires but they also have a faster rate of decline of FEV<sub>1</sub> (40). Little is known about what distinguishes frequent versus infrequent exacerbators. We do know that in stable patients with COPD, the systemic expression of the inflammation is suggested by studies showing increased plasma levels of biomarkers. There is also evidence of local respiratory inflammation measured by exhaled condensate (41). During exacerbation, there are changes observed in sputum, where increases in the level of IL-6, IL-8, and TNF- $\alpha$  suggest an intense inflammatory burst (41). Presumably, the circulating level of these cytokines could also change during an exacerbation, representing a systemic involvement of an initial respiratory event. However, there are no studies providing conclusive evidence of this mechanism. One fact is clear: Elucidation of the mechanisms responsible for the frequent-exacerbator phenotype must be undertaken so that we can develop appropriate therapeutic strategies.

## MULTIDIMENSIONAL ASSESSMENT

FEV<sub>1</sub> fails to adequately represent all of the respiratory and systemic manifestations of the disease. For example, FEV<sub>1</sub> correlates weakly with dyspnea (20), and the change in FEV<sub>1</sub> has been shown to have different characteristics from the rate of decline of health status in at least one drug trial (42). Prospective observational studies of patients with COPD have found that dyspnea and health status scores predict mortality better than FEV<sub>1</sub>. Thus, although FEV<sub>1</sub> is important to obtain and essential in the staging of any patient with COPD, the addition of other variables provide useful information to more comprehensively

help evaluate patients with COPD. The potential variables should correlate independently with prognosis in COPD, should be easily measurable, and should serve as surrogate for other potentially important variables. In a recent report, the multidimensional index that includes BMI (B), degree of airflow obstruction (O), dyspnea score (D), and exercise endurance measured with the 6-min-walk distance (E) (BODE index), was a better predictor of mortality than FEV<sub>1</sub> (43). The incorporation of various phenotypic elements into one integrative scoring system is of practical advantage because it allows us to group patients according to their prognosis. In addition, the BODE index could provide a surrogate tool to determine outcome because all four components of the index can potentially be improved by therapy.

## CLINICAL IMPLICATIONS

The degree of airflow remains the defining characteristic of COPD and thus its most important phenotypic expression. However, there is sufficient evidence to support the need to consider several phenotypic expressions in the characterization of patients with COPD (Table 1). These include the degree, type, and distribution of emphysema and its physiologic expressions as measured by DL<sub>CO</sub>; the degree of hyperinflation expressed by the IC and the IC/TLC; the presence of abnormal gas exchange (hypoxia and hypercapnia); the presence of systemic involvement as measured by the BMI; the exercise capacity, whether measured in the laboratory (peak oxygen uptake) or in the field (6-min walk test); and the degree of functional dyspnea. They can practically be integrated into multidimensional tools, such as the BODE index, which are capable of providing a more comprehensive evaluation of the patients. Finally, the overall impact of the disease on patient perception can be integrated by measuring the health-related quality of life. The determination of these phenotypic characteristics is not only scientifically interesting but is also clinically important because they confer prognostic value and, more importantly, they determine response to therapy. Oxygen for hypoxemic patients, noninvasive mechanical ventilation in patients with hypercapnic respiratory failure and acidosis, lung volume reduction in patients with upper lobe disease, and poor exercise capacity have shown to decrease mortality. In addition, pulmonary rehabilitation has improved outcome in symptomatic patients with decreased exercise capacity, whereas nutrition optimization has had an impact on mortality.

**TABLE 1. PHENOTYPES AND AVAILABLE TREATMENTS**

Phenotype	Available Treatments
Sex	
Airflow obstruction	BD, ICS
Emphysema hyperinflation	BD, LVR
Hypoxemia	Oxygen
Systemic involvement BODE index	ICS, rehabilitation Nutrition LVR
Exacerbator	BD, ICS Antibiotics SCS during exacerbations
Comorbidities	Specific therapy
Cardiovascular	
Osteoporosis	
Anemia	
Depression	

*Definition of abbreviations:* BD = bronchodilators; BODE = Body mass index, degree of airflow Obstruction, Dyspnea score, and Exercise endurance measured with the 6-min walk distance; ICS = inhaled corticosteroids; LVR = left ventricular reduction; SCS = systemic corticosteroids.

TABLE 2. OTHER POSSIBLE PHENOTYPE CHARACTERIZERS

Markers
Sputum
Breath condensate
Serum
Tissue
Radiologic
Airway and parenchymal compromise
Positron emission tomography
Psychologic profile
Control of breathing

## FUTURE DIRECTIONS

The moment has come to move from a disease expressed solely by the degree of airflow limitation that it generates to a much broader and resourceful characterization of COPD. Recent advances in the application of basic science resources to the understanding of clinical expressions of disease through genomics, proteomics, and metabonomics, or neglected aspects that may explain the clinical course of certain patients, such as their psychologic background and milieu, will increase our understanding and provide a more solid scientific rationale to the phenotypic characterization of patients with COPD (Table 2). Such understanding will not only help explain the manifestations and course of the disease in particular patients but also help select for specific therapies. The hope is that, coupled with primary and secondary prevention, we can reverse the current epidemic and improve the well-being of patients affected by COPD. The future is bright.

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Chronic obstructive pulmonary disease (COPD) is primarily a lung disease with important systemic consequences. These are associated with alterations in selected serum biomarkers (SM). A systematic analysis of multiple SM and their correlation with clinical parameters of COPD is possible with new protein microarray platform (PMP) technology.

We studied 47 patients (65% male) with COPD ( $FEV_1 < 55\%$ ) and 48 matched control subjects. We measured anthropometrics, dyspnea (Medical Research Council [MRC] scale), pulmonary function tests, 6-min walk distance (6MWD), body mass index, obstruction, dyspnea, exercise (BODE) index, and number of exacerbations. We explored the association of these outcomes with the results of 143 SM, measured by rolling circle amplification using PMP. The SM were tested for significance by univariate analysis, and clustered ( $n = 30$ ) by variable clustering. The clusters were ranked by computing the predictiveness of each cluster for COPD (partial least square discriminant analysis). From the eight “best predictive” clusters, we selected two to three SM based on their pathophysiologic profile (chemoattractants, inflammation, tissue destruction and repair) and by their statistical significance.

A panel of 25 SM had a significant correlation ( $p \leq 0.01$ ) with  $FEV_1$ ,  $DL_{CO}$ , 6MWD, BODE index (Figure 1) and exacerbation frequency.

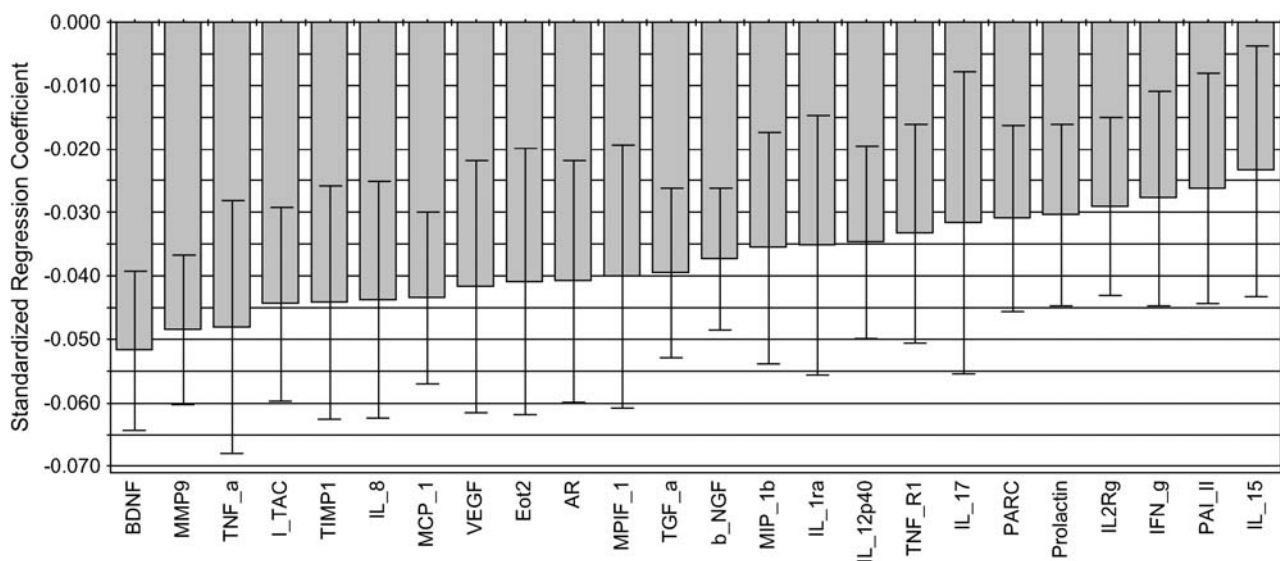
We conclude that SM using PMP technology can be used in the diagnosis and characterization of COPD. It may also be useful to assess response to treatment and to develop novel drug targets.

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## Use of Proteomic Patterns of Serum Biomarkers in Patients with Chronic Obstructive Pulmonary Disease

### Correlation with Clinical Parameters

Victor Pinto-Plata, John Toso, Kwan Lee, John Bilello, Hana Mullerova, Mary De Souza, Rupert Vessey, and Bartolome Celli



**Figure 1.** Association of the selected biomarker panel with the  $FEV_1$ . The size of the bar in the graph indicates the magnitude of the regression coefficients and the 95% confidence interval is also indicated for each bar. If the confidence interval includes zero, the associated biomarker is “not significant.” The overall regression model was significant by a permutation test ( $p < 0.01$ ).