Natural History of Emphysema

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Chronic obstructive pulmonary disease (COPD) is a progressive disease with studies of disease progression generally focusing on measures of airflow and mortality. In nonsmokers, maximal lung function is attained around age 15 to 25 years, and after a variable plateau phase, subsequently declines at approximately 20 to 25 ml/year. Smoking may reduce the maximal FEV₁ achieved, shorten or eliminate the plateau phase, and may accelerate the rate of decline in lung function in a dose-dependent manner. Some smokers are predisposed to more rapid declines in lung function than others, and recent reports suggest that females may be at higher risk of lung damage related to smoke exposure than males. Progressive deterioration in dyspnea, functional status, and health-related quality of life (HRQL) in patients with COPD is well known, but the magnitude and rate of decline and its association with severity of airflow obstruction remains poorly defined. Many studies have identified pulmonary function, in particular the FEV₁, as the single best predictor of survival. An impaired diffusing capacity and overall impairment in functional status have also been associated with impaired survival in COPD. The National Emphysema Treatment Trial has provided additional insight into these features in a large, well-characterized group of patients with severe airflow obstruction and structural emphysema.

Keywords: emphysema; natural history; survival; pulmonary function; quality of life

Chronic obstructive pulmonary disease (COPD) has been variously defined by the American Thoracic Society/European Respiratory Society (1) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2). These definitions emphasize that airflow limitation hallmarks COPD, which is characterized as partially reversible, usually progressive, associated with abnormal lung inflammation in response to noxious particles or gases, and most importantly, preventable and treatable. Current COPD guidelines define airflow limitation as being present when the ratio between forced expiratory flow in one second (FEV₁) and forced vital capacity (FVC) is less than 70% (1, 2). This definition is easy to remember, although there is concern that the use of a “fixed” ratio may lead to under- and over-estimation in younger and older populations, respectively (3, 4). Although earlier definitions included segregation of patients into different phenotypes, including chronic bronchitis and emphysema (5), more recent guidelines have moved away from this artificial separation, favoring the more

descriptive term, COPD (1, 2). In this article we have tried to focus on the emphysematous phenotype when data are available.

PREVALENCE

Higgins and Thom reported (6) that the prevalence of emphysema ranges from 4 to 6% of adult white males and 1 to 3% of white females, whereas Bang reports a prevalence of COPD of 3.7% in African American males and 6.7% in African American females (7). A recent meta-analysis by Halbert and colleagues suggests that the prevalence of COPD is higher among males than females, among smokers and former smokers than nonsmokers, and among those over 40 years old than those under 40 (8). However, the prevalence of COPD can vary significantly for a given population, depending upon which definition is used (3, 9).

PROGRESSION OF EMPHYSEMA: NATURAL HISTORY AND RISK FACTORS

As noted by international guidelines, COPD is a progressive disease (1, 2). Studies of disease progression have generally been limited to measures of airflow and mortality. Increasingly, worsening of symptoms or health status, as well as the appearance of co-morbidities, have been investigated.

Spirometric Progression

Numerous studies have focused on FEV₁ decline over time. Once maximal lung function is attained around age 15 to 25 years (10–15), it remains relatively constant for approximately a decade (the “plateau phase”). In nonsmokers, lung function subsequently declines by approximately 20 to 25 ml/year (16), and roughly 1 liter is lost over the next five decades. Reports differ on whether this decline is linear, and it has been suggested that the decline may accelerate with age (13, 15, 17, 18). Smoking impacts the natural history of pulmonary function in numerous ways. Several lines of evidence suggest that smoking may reduce the maximal FEV₁ achieved, including passive smoking, which may begin *in utero* (19, 20) or early childhood (21–24), as well as smoking during adolescence (25–27). Smoking may shorten the plateau phase (11, 28–30) or, in some instances, completely eliminate it (28). Finally, smoking accelerates the rate of decline in lung function (10, 14–17, 28, 31), as extensively reviewed elsewhere (32). Fletcher and coworkers (16) demonstrated that smokers have a steeper decline in pulmonary function than nonsmokers. The results of the Lung Health Study confirmed in a large, longitudinal study that smoking was associated with an accelerated decline in lung function (33). Interestingly, some smokers are predisposed to more rapid declines in lung function (“rapid decliners”) than others (“slow decliners”) (34), with large inter-individual differences in the rates of FEV₁ decline. Those with pre-existing airways obstruction have been suggested to be at the highest risk of “accelerated decline” (the so called “horse racing effect”) (16, 35). Further, it has been suggested that there is a “dose-response” relationship between the number of “pack-years” smoked and lung function decline (16, 36–38). It is also

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not clear whether the decline is linear in smokers or whether it occurs in a step-wise manner. Data on disease progression specific to emphysema are few, although the National Emphysema Treatment Trial (NETT) provides some insight with respect to deterioration in FEV₁ (Figure 1) (48). A deterioration over 2 years is notable, with significant inter-individual variability.

Whether consequences of smoke exposure are influenced by sex remains controversial (25, 36, 39–41), as recently reviewed (35). Recent reports suggest that females are at higher risk of lung damage related to smoke exposure than males (25, 42–44). The responsible physiological mechanisms are felt to be related to the structural development of lungs or hormonal homeostasis. Reports have suggested that females exposed to smoke during adolescence may be at an increased risk of having a lower maximal FEV₁ (25), developing early onset COPD because of a more rapid decline in FEV₁ (42, 43), and having a higher rate of bronchial hyperreactivity (44). Underlying genetic susceptibility has been touted as a possible reason to explain the fact that only 10 to 20% of smokers develop significant obstructive airways disease (45). However, other than α_1 -antitrypsin deficiency, there are no other convincing genetic associations (46). Since the prevalence of the relevant α_1 -antitrypsin variants is low, the proportion of emphysema attributable to this gene is approximately 1% (47).

Acute exacerbations of COPD are associated with significant reductions in pulmonary function, which may not completely resolve (49), and when recurrent, exacerbations have been associated with a more rapid decline in FEV₁ (50–52). Whether these concepts apply to a predominantly emphysematous population is not clear. The medically managed patients in the NETT experienced quite a bit of health care utilization, including hospitalizations and emergency room visits (53).

Exercise Capacity

Progressive deterioration in the functional status of patients with COPD is well known. How this translates to decreased exercise capacity, however, is less well studied. Peak oxygen uptake was reported to decline at a slope similar to the loss in FEV₁ in 137 males (mean age 69 years at initial testing) with moderately severe airflow obstruction (mean FEV₁ 45.9% predicted) (54) undergoing 5 years of sequential cardiopulmonary exercise testing (54). A different group examined long-

Figure 1. Change from baseline in FEV₁% predicted in non-high-risk medically treated patients in the National Emphysema Treatment Trial (NETT) who completed the procedure after 6, 12, or 24 months of follow-up (Reprinted by permission from 48).

term change in six-minute walk distance in a cohort of 294 patients with COPD (55). Over 5 years of follow-up the proportion of patients with a decline of greater than or equal to 54 m walked was higher in patients with worse airflow obstruction. The decline in FEV₁ over time was higher in those with milder airflow obstruction at baseline when compared with those with more severe obstruction. In patients with predominantly emphysematous disease, loss of exertional capacity has also been reported. The NETT investigators performed six-minute walk and maximal exercise testing using well defined methodology (56). Figure 2 illustrates change in six-minute walk in non-high-risk medically treated patients during early follow-up (Figure 2A) (48); a general decrease is noted, although significant heterogeneity is evident. Similar results are seen for changes in maximal watts achieved during longer term follow-up in all medically treated patients (Figure 2C) (57). It is evident that the natural history of exercise capacity is to decrease, particularly in patients with worse airflow obstruction, but the magnitude and rate of decline remains poorly defined.

Symptoms

Shortness of breath is a cardinal and often presenting symptom of COPD, particularly in those with emphysema (58). Dyspnea is typically progressive, has a complex relationship with severity of airflow obstruction, but only weakly correlates with FEV₁ (59). NETT investigators described that females exhibited greater breathlessness compared with males (60) as measured

Figure 2. (A) Change from baseline in maximal achieved six-minute walk test distance in non-high-risk medically managed patients in the NETT who completed the procedure after 6, 12, or 24 months of follow-up (48). (B) Longer-term change from baseline in maximal achieved watts during oxygen supplemented cardiopulmonary exercise testing in medically managed patients in the NETT (Reprinted by permission from 57).

by the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (61). In medically managed NETT patients, breathlessness has been shown to increase over 2 years of follow-up (Figure 3) (48).

Most patients with COPD develop cough and phlegm production at some point. Where that point lies along the COPD symptom continuum and whether it varies among different patients or populations is less clear. It is now better understood that the decline in FEV₁ and degree of mucus hypersecretion do not always parallel one another (62, 63). It has been reported that approximately 20 to 25% of smokers with chronic productive cough may have normal a FEV₁ and a similar proportion of smokers with low FEV₁ may not present with chronic productive cough (16). Patients with mucus hypersecretion may be at risk of more frequent COPD exacerbations (64, 65), which may lead to a more rapid decline in FEV₁ (30), and may be associated with more hospital admissions (66). In smokers without COPD, cough is associated with a greater impairment in quality of life (67) as well as greater mortality (68). Data assessing cough in COPD with more clearly defined clinical phenotypes are limited. Recently, one group has suggested that patients with emphysema with more bronchial wall abnormality on CT are more likely to complain of cough (69). The natural history of cough in patients with COPD remains unclear, although young adults with cough are more likely to be diagnosed with COPD over time (70).

Health Status

Increasing evidence suggests that health-related quality of life (HRQL) deteriorates with advancing COPD (71), although most studies have typically focused only on patients with advanced disease. Although data on patients with emphysema are more limited, it has been suggested that HRQL in patients with emphysema relates to the degree of airflow obstruction, the level of dyspnea, and capacity of effort and respiratory muscle pressures (72). NETT investigators examined HRQL and its predictors in randomized patients (73). In general HRQL was low and correlated weakly with the level of airflow obstruction, maximum work during exercise testing, and six-minute walk distance. Longitudinal data from the ISOLDE study demonstrated that patients with moderate and severe COPD had impairment in baseline HRQL that worsened during 3 years of follow-up (74). These investigators and others

have suggested that recurrent exacerbations lead to worsened impairment (75). Longitudinal data on patients with well-defined emphysema are scanty. The NETT investigators have provided preliminary insight on this topic (Figures 4A and 4B) (48, 57). It is evident that a worsening of disease-specific HRQL was noted in patients with severe emphysema. Furthermore, the magnitude of rise is higher than the widely accepted minimally accepted clinical difference in the St. George's Respiratory Questionnaire. The determinants of worsened disease-specific HRQL in severe emphysema remain unclear.

Emphysema Severity

It is evident that emphysema is a progressive disease, as attested to by worsening pulmonary function, exercise capacity, symptoms, and HRQL. A key question is the relationship of these parameters to structural markers of disease. The availability of imaging techniques has allowed assessment of progression in structural abnormalities. An early study in 22 patients with α_1 -antitrypsin deficiency related emphysema quantified lung density over 30 months (76). Lung density changes correlated with changes in health status but not FEV₁ or DLCO. More recently, a prospective study of 87 patients with emphysema (24 current smokers) examined over a thirty month period with quantitative chest computed tomography (77) found that changes in FEV₁ or DLCO did not correlate with changes in lung density over time, and the authors concluded that change in lung density was a more sensitive measure of emphysema progression than changes in pulmonary function parameters. More recently, the methodology to assess serial changes in lung density have been better defined (78). Future studies should provide a better sense of anatomical disease progression.

Mortality

Mortality, a key feature of disease progression, has been rising in COPD over the past three decades (79), during which time many authors have examined the natural history of COPD in an attempt to identify prognostic factors (80, 81). The vast majority of these studies have identified pulmonary function, in particular the FEV₁, as the single best predictor of survival (80–82). In the Intermittent Positive Pressure Breathing Trial (IPPB), in which a wide spectrum of patients with COPD without hypoxemia were recruited, baseline prebronchodilator FEV₁ and patient age were the best predictors of mortality (83, 84); survival was worst in patients with a postbronchodilator FEV₁ less than 30% predicted. An impaired diffusing capacity has been suggestive of a decreased survival in some studies (80).

Figure 3. Change from baseline in the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) among non-high-risk, medically managed NETT patients (Reprinted by permission from 48). A minimal clinically important improvement is a decrease in UCSD SOBQ of 5 points or more.

Figure 4. Change in St. George's Respiratory Questionnaire in all patients randomized to the medical arm of the NETT during 5 years of follow-up (Reprinted by permission from 57).

Overall impairment in functional status has been associated with impaired survival in COPD, with numerous investigators reporting worse survival in patients with COPD with a lesser exercise capacity (80, 85).

Pulmonary hypertension is present in a significant proportion of patients with advanced COPD and, although severe pulmonary hypertension is unusual (86, 87), it appears to independently influence survival (88). Nutritional status also strongly influences COPD prognosis (81). Recently, investigators have incorporated the multitude of clinical abnormalities in COPD into multidimensional indices (89). The most compelling of these, published by Celli and colleagues, is the BODE index, which reflects the body mass index (B), the degree of airflow obstruction (O), dyspnea (D), and the exercise capacity measured by the six-minute walk test (89).

The impact of the diagnosis of emphysema on prognosis in COPD has received limited attention. Burrows and colleagues studied 117 subjects with chronic airflow limitation (FEV_1 47.1–51.3% predicted) and characterized subjects as “asthmatic bronchitis” if they were atopic and had a minimal smoking history (< 10 pack-years), “typical COPD” if there was no asthma or atopy history along with a greater than 10 pack-year smoking history, and “mixed” if these features were not met (90). A significant difference in survival was noted favoring patients with asthmatic bronchitis. Mortality data specific to emphysema has been best characterized in the setting of α_1 -antitrypsin deficiency associated COPD. Three-year mortality has been reported to be less than 40% in those with an initial FEV_1 less than 30% predicted, compared with 93% when the FEV_1 was between 30 and 65% predicted in one early study

TABLE 1. SIGNIFICANT PREDICTORS IN MULTIVARIATE MORTALITY MODELS IN PATIENTS (n = 609) WITH SEVERE EMPHYSEMA (94)

Predictor	Model 1*			Model 2*		
	Hazard Ratio	(95% CI)	P Value	Hazard Ratio	(95% CI)	P Value
Age, yr						
70–83	1.64	(1.23–2.18)	0.001	1.72	(1.31–2.26)	< 0.001
40–69		Reference			Reference	
BMI (kg/m ²)						
High (> 28.1)	0.86	(0.62–1.21)	0.40	Not applicable (BODE component)		
Medium		Reference				
Low (< 21.4)	1.32	(0.98–1.78)	0.06			
Oxygen use (rest, exercise, or sleeping)						
Yes	1.46	(1.02–2.10)	0.04	1.40	(0.98–2.01)	0.07
No		Reference			Reference	
Hemoglobin (g/dL)						
9.1–13.3	1.34	(0.97–1.85)	0.08	1.38	(1.00–1.89)	0.05
13.4–19.1		Reference			Reference	
SOBQ score						
79–109	1.39	(0.98–1.97)	0.06	Not applicable (BODE component)		
9–78		Reference				
Total lung capacity (% predicted)						
140–203	0.68	(0.46–1.00)	0.05	0.69	(0.47–1.01)	0.06
95–139		Reference			Reference	
Residual volume (% predicted)						
262–412	1.57	(1.03–2.39)	0.04	1.56	(1.04–2.37)	0.03
97–261		Reference			Reference	
D _{LCO}						
6–21	1.34	(0.99–1.82)	0.06	1.36	(1.01–1.84)	0.04
22–68		Reference			Reference	
Maximal CPET workload (W)						
Low†	1.54	(1.17–2.03)	0.002	1.48	(1.12–1.94)	0.006
High†		Reference			Reference	
Difference in % emphysema (upper lung-lower lung)						
–40.4 to –0.8	1.74	(1.19–2.57)	0.005	1.80	(1.22–2.66)	0.003
–0.7 to 63.6		Reference			Reference	
Missing	0.84	(0.55–1.28)	0.41	0.86	(0.57–1.31)	0.49
Perfusion ratio						
0.04–0.14	1.57	(1.13–2.17)	0.007	1.53	(1.11–2.12)	0.01
0.15–3.13		Reference			Reference	
Modified BODE index‡						
7–10		Not applicable§§		1.48	(1.07–2.05)	0.02
1–6					Reference	

Definition of abbreviations: BMI = body mass index; CI = confidence interval; CPET = cardiopulmonary exercise testing; D_{LCO} = diffusing capacity for carbon monoxide; SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

Results are shown for those variables that were significant predictors at the $P \leq 0.05$ level in either model. Model 2 was the same as Model 1 except that the modified BODE index replaced its components.

* All variables include BMI; kg; m²; St. George's Respiratory Questionnaire; SOBQ; FEV_1 ; ratio of inspiratory capacity to total lung capacity; D_{LCO}; maximum inspiratory pressure; maximum expiratory pressure; PaO₂; PaCO₂; six-minute walk test; and CPET.

† Low exercise is defined as a maximal workload at or below the sex-specific 40th percentile (25 W for females and 40 W for males; high exercise is defined as a workload above this threshold).

‡ Components of the modified BODE index are: BMI, FEV_1 , UCSB SOBQ score, and 6MWT distance.

§ $P = 0.012$ for the four components for the modified BODE index.

Figure 5. Kaplan-Meier estimates of the probability of death as a function of number of years after randomization for medically treated patients segregated by age. The *P* value was derived by the log rank test for the comparison between subgroups over a median follow-up period of 3.9 years (Reprinted by permission from Reference 94).

(91). Separate analyses support that prognosis in emphysema associated with α_1 -antitrypsin deficiency worsens when the FEV₁% predicted falls below 25 to 30% (92, 93). NETT investigators have recently published mortality models examining the survival characteristics of the medically treated patients (94). Table 1 enumerates the factors associated with survival in severe emphysema. These data support the notion that many of the factors prognostic in COPD are also prognostic in patients with emphysema. Age is a strong predictor (Figure 5), as are numerous physiological features. Importantly, the BODE index is strongly predictive in this population (Figure 6), even with the more severe baseline level of airflow obstruction noted in the NETT patients (95). The amount of emphysema and its distribution were also independent prognostic factors, as was the maximal exercise capacity. A subanalysis of mortality as a function of structural features in histologic samples from NETT patients confirms that airway mucous is a strong factor influencing long-term survival (Figure 7) (95).

Figure 6. Kaplan-Meier estimates of the probability of death as a function of number of years after randomization for medically treated patients segregated by modified BODE index. The *P* value was derived by the log rank test for the comparison between subgroups over a median follow-up period of 3.9 years (Reprinted by permission from Reference 94).

Figure 7. Kaplan Meier survival plot of the 101 cases of severe (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 3) and very severe (GOLD stage 4) chronic obstructive pulmonary disease, indicating that median survival was shortened in the quartile with the most severe occlusion of the fully expanded lumen (HR [hazard ratio], 3.28; 95% confidence interval, 1.55 to 6.92; *P* = 0.002) (Reprinted by permission from Reference 95).

CONCLUSIONS

COPD is a progressive disease with one of its pathophysiologic bases reflecting emphysematous destruction. Review of the data suggests that emphysema is a similarly progressive disorder associated with spirometric progression, symptomatic worsening, health status worsening, and impaired survival. The NETT has provided additional insight into these features in a large, well-characterized group of patients with severe airflow obstruction and structural emphysema.

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