Exacerbations in Chronic Obstructive Pulmonary Disease
Do They Contribute to Disease Progression?

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The impact of chronic obstructive pulmonary disease (COPD) exacerbations on decline in FEV_1 has been a controversial topic for decades. We will review some of the key studies in this area and discuss potential contributors to inconsistent results of these studies. Dissecting the heterogeneous COPD syndrome into meaningful subtypes and assessing the genetic and environmental influences on COPD-related phenotypes such as exacerbation frequency could clarify the impact of exacerbations on the natural history of COPD.

Keywords: chronic obstructive pulmonary disease; exacerbations; natural history; heterogeneity; genetics

Exacerbations are a major cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD) (1). COPD exacerbations have broad impact on affected individuals, including reduction in quality of life (2). Although exacerbations have been clearly demonstrated to occur more frequently as COPD becomes more severe, the frequency of exacerbations varies widely among individuals with similar degrees of COPD severity. A persistently controversial issue has been whether COPD exacerbations are a cause of FEV_1 decline, or whether they are simply an effect of more severe disease.

We will review some of the key studies that have assessed the impact of COPD exacerbations on lung function decline, and we will consider how the heterogeneity of COPD could contribute to differential susceptibility to develop exacerbations.

DESCRIPTION OF SEVEN KEY STUDIES

In this section, we will compare the study designs and main findings for seven key studies that have examined the relationship between COPD exacerbations and lung function decline.

In Sheffield, United Kingdom, Howard studied a cohort of 159 industrial working men who were not selected for respiratory disease (3). Most of the subjects were cigarette smokers, but 27 nonsmokers were included. The mean age of the subjects was 42 years at the beginning of the study. The cohort was followed longitudinally for 11 years, with visits at 0, 6, 9, 10, and 11 years. The primary pulmonary function parameter was $FEV_{0.75}$, and slopes of change in $FEV_{0.75}$ were determined by regression for each subject. Subjects with exacerbations were defined as those individuals experiencing two or more chest illnesses in the previous 3 years.

Surprisingly, there was no relationship of $FEV_{0.75}$ decline to ongoing cigarette smoking. However, decline in $FEV_{0.75}$ was greater among subjects with lower $FEV_{0.75}$ at the start of the study in this largely healthy cohort. In addition, greater decline in $FEV_{0.75}$ was observed at older ages.

The overall rate of chest illnesses declined after 1962, with one potential explanation being reduced environmental air pollution in the United Kingdom. There were 31 men who experienced chest illnesses for at least 2 consecutive years that kept them off work; they had lower $FEV_{0.75}$ values and higher rates of $FEV_{0.75}$ decline. However, only nine men acquired frequent chest illnesses; six already had low $FEV_{0.75}$, suggesting that chest illnesses were the effect rather than cause of low $FEV_{0.75}$. Thus, Howard concluded that chest illnesses did not contribute to pulmonary function decline.

Bates led a study of 216 male smokers with chronic bronchitis from four Canadian Veterans Affairs centers (4). These men had no other chest diseases, and they were still working. This longitudinal cohort was monitored for 10 years. The primary pulmonary function phenotypes were $FEV_{0.75}$ and maximal midexpiratory flow (MMEF) rate. Their baseline values for these phenotypes appeared mildly reduced, on average. Subjects were monitored with pulmonary function tests monthly for the first year, then yearly for the remainder of the study. At baseline evaluation, exacerbations in the previous 3 years were assessed by a questionnaire. At each follow-up visit, a questionnaire about chest infections that had occurred since the previous visit was completed.

A subpopulation of 31 subjects with large changes in $FEV_{0.75}$, MMEF, VC, or D_{LCO} (diffusion capacity of carbon monoxide) was compared with 29 subjects with minimal changes in these parameters to assess the impact of chest infections on lung function decline. Greater smoking intensity and increased cough and dyspnea were observed among rapid decliners. However, there was no difference in incidence of chest infections or number of days per year with chest infections in rapid versus slow decliners, suggesting that exacerbations did not contribute to pulmonary function decline.

Fletcher and colleagues performed a classic study of 792 industrial and management working men from West London (United Kingdom), who were not selected for respiratory disease (5, 6). This cohort was monitored longitudinally for 8 years, with visits every 6 months to perform pulmonary function tests and to complete questionnaires. They used FEV_1 as their primary pulmonary function outcome; slopes of change in FEV_1 were determined by regression for each subject. Exacerbations were determined by questionnaire every 6 months; some sputum samples were also assessed for purulence by visual inspection to assess exacerbations more objectively.

Several fundamental observations about FEV_1 decline were made from this study. The investigators noted that FEV_1 decline typically occurs smoothly and continuously, and that the rate of decline accelerates slightly with aging. They concluded that nonsmokers lose FEV_1 slowly; many smokers lose FEV_1 at the same rate as nonsmokers. They also noted that FEV_1 decline is a continuum—there are not two discrete groups of rapid decliners and nondecliners—supporting variable susceptibility to the effects of tobacco smoking.

In terms of the impact of acute chest illnesses on FEV_1 decline, after adjusting for baseline FEV_1, smoking, age, and

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height, there was no independent relationship between FEV_1 decline and indices of respiratory infections. In addition, the loss of FEV_1 for individual men over a particular 6-month period was not influenced by the development of a chest cold, chest illness, or increased sputum purulence. They concluded that bronchial infections do not cause irreversible airflow obstruction.

Kanner and colleagues performed a study in Utah that included 84 white individuals with chronic bronchitis and/or emphysema (7). Most (84.5%), but not all, of their study participants were men. Subjects with asthma were not excluded, and 17% of the subjects were nonsmokers. A broad range of FEV_1 and FEV_1/FVC values were observed, although they were not reported as % predicted. Subjects in this cohort were monitored for at least 2 years with clinic visits, including completion of a standard questionnaire four to six times per year and weekly phone calls to assess for respiratory illnesses. They used post-bronchodilator FEV_1 and FVC as their primary pulmonary function measurements. At least five separate spirometric measurements were required for a particular subject to be included in the assessment of lung function decline.

Exacerbations were defined as lower respiratory tract illnesses (LRIs) with the following characteristics: new development or increase in symptoms of cough, dyspnea, wheezing, or sputum purulence. Multivariate analysis of determinants of FEV_1 decline was performed. An increased frequency of LRIs per year was significantly associated with FEV_1 decline. Lower α_1-antitrypsin levels were also associated with FEV_1 decline; surprisingly, four protease inhibitor (PI) ZZ subjects were included in this small cohort. Increased smoking intensity and increased bronchodilator responsiveness were also independent predictors of FEV_1 decline. There was no association of FEV_1 decline with "influenza-like illnesses" or other respiratory illnesses (asthma, pleurisy, or pneumonia). The authors concluded that increased frequency of LRIs was associated with accelerated FEV_1 decline. The occurrence of similar frequencies of LRIs among groups stratified by pulmonary function suggested that this effect was independent of COPD severity.

The Lung Health Study provided the largest cohort to examine the impact of exacerbations on FEV_1 decline (8). Kanner and colleagues analyzed 5,887 smokers from the United States and Canada with an FEV_1/FVC less than 0.7 and an FEV_1 in the range of 55 to 90% predicted at study initiation. This longitudinal cohort had been monitored for 5 years at the time of their analysis. The authors used decline in FEV_1 as their primary outcome, based on annual spirometry. COPD exacerbations were defined based on self-reported LRIs from an annual questionnaire: bronchitis, pneumonia, influenza, or a chest cold requiring a physician visit in the preceding year.

The overall rate of LRIs was 0.24 LRIs per subject per year. Predictors of increased LRI rate were female sex, an LRI in the previous year, low FEV_1, and chronic bronchitis. In a stratified analysis, continuous smokers had more LRIs than sustained quitters. In addition, LRIs were associated with more rapid FEV_1 decline in continuous smokers and intermittent quitters, but not in sustained quitters. The excess loss of FEV_1 resulting from one LRI/year was 7 ml/year in continuous or intermittent smokers.

In East London, Donaldson and colleagues studied 109 subjects with moderate to severe COPD (median FEV_1, 38% predicted) from the United Kingdom (9). This cohort was monitored longitudinally for 4 years. All 109 subjects recorded daily peak expiratory flow rate on diary cards, and 32 subjects also recorded daily FEV_1 on diary cards. Exacerbations were defined by at least 2 consecutive days of at least two of the three major symptoms (increased dyspnea, sputum purulence, or sputum volume) or any one major symptom plus a minor symptom (increased nasal discharge, wheezing, sore throat, cough, or fever) as recorded on diary cards. The diary cards were reviewed every 3 months; some additional exacerbations were identified at clinic visits or hospital admissions. Subjects were designated as frequent or infrequent exacerbators based on whether they were above or below the median exacerbation rate per year.

With this intensive degree of follow-up, a high rate of exacerbations was observed; 100 of 109 subjects had at least one exacerbation, and the median exacerbation frequency was 2.5 exacerbations per year. The authors noted that the number of exacerbations in the first year was highly correlated with the number of exacerbations in subsequent years. Frequent and infrequent exacerbators had similar age, baseline FEV_1, sex, and smoking intensity; the frequent exacerbator group tended to have more current smokers and increased respiratory symptoms. Sixteen frequent exacerbators (-40.1 ml/yr) had faster FEV_1 decline than 16 infrequent exacerbators (-32.1 ml/yr); a similar pattern was observed for peak expiratory flow rate.

In the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, Spencer and colleagues studied 613 nonasthmatic current or ex-smokers with COPD participating in a randomized clinical trial of fluticasone treatment in the United Kingdom (10). Participants were required to have baseline FEV_1 greater than 0.8 L but less than 85% predicted, and baseline FEV_1/FVC less than 0.7. This longitudinal cohort was monitored for 3 years in a clinical trial; this analysis focused primarily on decline in quality of life, but decline in FEV_1 was also assessed. Pulmonary function tests included spirometry every 3 months; both treatment arms were analyzed together. Exacerbations, assessed at 3-month intervals, were defined by self-report of chest problems requiring treatment with antibiotics and/or oral steroids. The median exacerbation rate was 1.65/year. Subjects were designated as having no exacerbations (n = 91), infrequent exacerbations (below median exacerbation rate but more than 0, n = 285), or frequent exacerbations (above median exacerbation rate, n = 235).

They found a highly significant relationship between baseline FEV_1 and exacerbation frequency; FEV_1 was 55 ± 15% predicted in subjects with no exacerbations and 49 ± 15% predicted in subjects with at least one exacerbation ($P = 0.001$), and FEV_1 was 53 ± 15% predicted in subjects below the median exacerbation frequency and 45 ± 13% predicted in subjects above the median exacerbation frequency ($P < 0.0001$).

The investigators found that FEV_1 decline was 50 ml/year in subjects with no exacerbations and 55 ml/year in subjects with at least one exacerbation (P = not significant). In addition, FEV_1 decline was 55 ml/year in subjects with infrequent exacerbations and 54 ml/year in subjects with frequent exacerbations (P = not significant). Thus, no significant effect of exacerbations on FEV_1 decline could be demonstrated.

INTERPRETATION OF PREVIOUS STUDIES

Of these seven key studies, four found no impact of exacerbations on FEV_1 (or $FEV_{0.75}$) decline, whereas three found a significant relationship (Table 1). What are the possible explanations for these discordant results? First, there are substantial differences in study populations in these seven studies. In general, older studies were less likely to find an effect of exacerbations: It is not clear that COPD exacerbations or even COPD itself were clinically, epidemiologically, and pathologically the same in 1960 and 2000. Second, studies of subjects with COPD were more likely to find an effect of exacerbations on FEV_1 decline than studies of subjects unselected for respiratory disease. This raises the question of whether someone who does not have COPD can have a COPD exacerbation. Studies with cohorts of largely healthy subjects may have been examining the determinants of respiratory infections rather than COPD

TABLE 1. DO CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS CONTRIBUTE TO FEV_1 DECLINE?

Study (Lead Author)	Date Cohort Was Completed	Sample Size	COPD Status of Participants	Smoking Status of Participants	Relationship of Exacerbations to FEV Decline?
Sheffield Study (Howard)	1967	159	Unselected	17% Nonsmokers	No
Canadian VA Study (Bates)	1970	216	Chronic bronchitis	Smokers	No
West London Study (Fletcher)	1969	792	Unselected	10% Nonsmokers	No
Utah Study of COPD Epidemiology (Kanner)	1973	84	Chronic bronchitis and/or emphysema: range of severity	17% Nonsmokers	Yes
Lung Health Study (Kanner)	1994	5,887	Mild–moderate COPD	Smokers; stratified analysis performed	Yes
East London COPD Exacerbation Study (Donaldson)	1998	109	Moderate–severe COPD	Smokers; stratified analysis performed	Yes
ISOLDE (Spencer)	1998	613	COPD: range of severity	Smokers	No

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ISOLDE = Inhaled Steroids in Obstructive Lung Disease in Europe.

exacerbations. Third, many of these key studies have small samples. However, there was no clear difference in effect for larger studies. Fourth, loss to follow-up of frequent exacerbators could contribute to the difficulty in demonstrating a relationship between exacerbations and FEV_1 decline. For example, in the ISOLDE trial discussed above, subjects who failed to complete the study had more frequent exacerbations and more rapid decline in FEV_1 (11). Fifth, there was variable inclusion of nonsmokers and smoking status stratification. It is possible that smoking status stratification, as performed in the Lung Health Study, could have led to more consistent evidence for an effect of exacerbations on FEV_1 decline. Sixth, different criteria to assess exacerbations were used in different studies; many of these studies used questionnaire responses to assess exacerbations, often with a large recall interval which could reduce accuracy. Finally, widely variable criteria were used to define an exacerbation. It is unclear whether, for example, pneumonia should be included as a COPD exacerbation. Fewer exacerbations were reported among patients with COPD treated with salmeterol/fluticasone in the recent TORCH study, but a higher rate of pneumonia was also found in this group (12). Of note, these seven studies often used relatively simple statistical analysis approaches; more complex longitudinal data analysis methods potentially could provide more consistent results among studies (13).

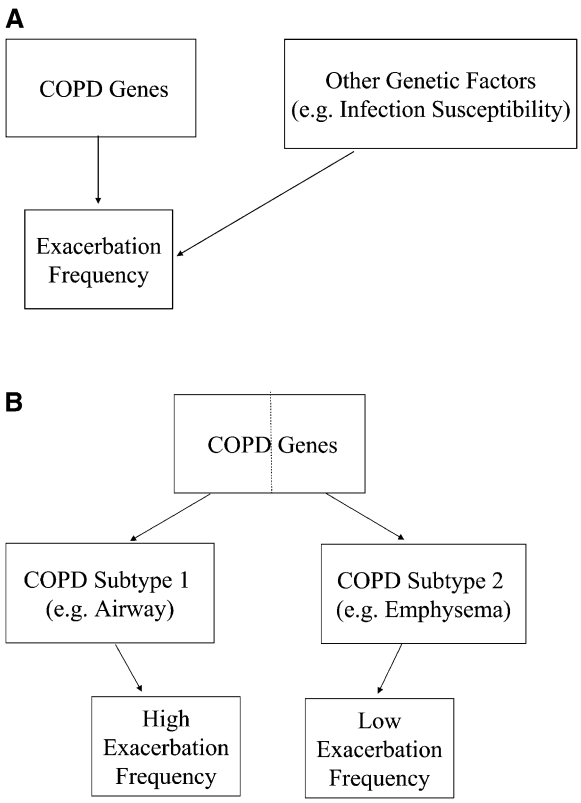

Figure 1. (*A*) Additional factor model. Variation in chronic obstructive pulmonary disease (COPD) exacerbation frequency could be unrelated to differences in the type of COPD, but rather to independent factors, such as genetic or environmental determinants of susceptibility to respiratory infections. (*B*) COPD heterogeneity model. Variation in COPD exacerbation frequency could relate to specific subtypes of COPD. For example, subjects with emphysema-predominant disease could have a different exacerbation frequency compared with subjects with airway-predominant disease.

MODELS FOR THE VARIABLE SUSCEPTIBILITY TO COPD EXACERBATIONS

Perhaps the most likely explanation for the divergent study results noted above is the inherent heterogeneity of COPD. COPD is a complex syndrome, influenced by both genetic and environmental factors, with component processes of parenchymal destruction (emphysema) and small airway disease. These component processes could be used to define COPD subtypes (e.g., emphysema predominant vs. airway predominant) that may have different genetic determinants, environmental influences, and disease pathophysiology. It may be more accurate to consider these component processes as independent (or even related) pathophysiologic pathways that overlap to varying degrees in different subjects with COPD. COPD subtypes could be defined using various parameters, such as differences in radiologic, physiologic, or genetic characteristics. For the purposes of this discussion, we will focus on potential differences in genetic predisposition to different COPD subtypes. In addition to subtypes of COPD, a variety of COPD-related phenotypes are part of the COPD syndrome, including exacerbations, functional impairment, emphysema distribution, and COPD severity. These COPD-related phenotypes may differ within COPD subtypes, or they may have independent genetic, environmental, and developmental influences.

The variable frequency of exacerbations needs to be investigated and understood within this context. We will consider two potential etiologic models for this COPD-related phenotype. The additional factor model (Figure 1A) is based on independent factors (genetics in this depiction) relating to susceptibility to infections that influence variability in exacerbation frequency, rather than differences in COPD subtypes. Alternatively, the COPD heterogeneity model (Figure 1B) is based on distinct subtypes of COPD (potentially influenced by different sets of

genes). There could be different exacerbation frequencies within COPD subtypes.

Several approaches could be used to determine which, if either, of these models is correct. One approach is to identify genetic determinants of COPD without attempting to divide subjects with COPD into subtypes, then to assess the relationship of such genetic determinants to COPD-related phenotypes. This approach has been limited by the lack of definitive identification of novel COPD susceptibility genes other than α_1-antitrypsin deficiency. A second approach is to identify genetic determinants of COPD subtypes (e.g., emphysema vs. airway), then assess COPD-related phenotypes in those subtypes. This approach has been limited by the paucity of large studies with comprehensive chest computed tomography characterization of emphysema and airway disease. A third approach involves identifying genetic determinants of COPD-related phenotypes (e.g., functional impairment, exacerbation frequency) directly, then determining whether or not they are COPD susceptibility genes. Several candidate gene association studies have assessed the determinants of COPD-related phenotypes, but it is not yet clear whether these associations represent additional factors influencing COPD or distinct subtypes of COPD.

EXAMPLES OF STUDIES OF COPD-RELATED PHENOTYPES

Celli and colleagues' BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index emphasizes that dyspnea and exercise capacity provide additional information about COPD severity beyond FEV_1 level (14). This raises the question: Are there genetic determinants of functional impairment in COPD independent of FEV_1? Hersh and colleagues used a candidate gene approach to study genetic determinants of functional impairment in COPD (15). They studied 304 National Emphysema Treatment Trial (NETT) subjects, who were randomly divided into a test set (n = 150) and a replication set (n = 154). They genotyped 80 variants in 22 candidate genes selected from previous genetic association studies and models of disease pathophysiology. Phenotypes included the following: exercise capacity (six-minute-walk distance and maximum work), respiratory symptoms (dyspnea), and the BODE index. Genetic association analysis was performed with multiple regression models, adjusting for FEV_1. The authors required significance levels of $P < 0.1$ in the test set and $P < 0.05$ in the replication set to at least one marker for a gene to be considered positively associated with a particular phenotype.

Genetic variants in several candidate genes, including microsomal epoxide hydrolase (EPHX1), surfactant protein B (SFTPB), and latent transforming growth factor binding protein 4 (LTBP4), influenced exercise capacity independent of FEV_1. Genetic variants in transforming growth factor-β1 (TGFB1) influenced symptoms of dyspnea independent of FEV_1. However, further analysis of genetic determinants of functional impairment in other COPD populations will be required to determine whether these associations represent disease subtypes or disease-modifying factors.

Studies of genetic determinants of COPD exacerbations have not been widely performed. However, Takabatake and colleagues recently reported a study of 276 male Japanese subjects with COPD; all were ex-smokers (16). They studied four single nucleotide polymorphisms (SNPs) in three chemokine genes: CCL11, CCL5, and CCL1. They defined COPD exacerbations as follows: (*1*) change in sputum volume or color; (*2*) increased dyspnea, cough, or fever; (*3*) hospitalization and/or antibiotic prescription; and (*4*) increased C-reactive protein, increased white blood cell count, or radiographic infiltrate. They performed association analysis with logistic regression to adjust for age, smoking, and FEV_1. In an analysis of 2 years of retrospective data, having frequent exacerbations was associated with CCL1 SNP rs2282691 in a dominant model. This SNP was also associated with mortality in a prospective study of this same cohort. More studies of the genetic determinants of exacerbation frequency will be required to replicate these findings and to identify additional COPD exacerbation genetic determinants.

FUTURE DIRECTIONS FOR RESEARCH

Despite decades of investigation, the impact of COPD exacerbations on FEV_1 decline remains uncertain. Although alternative metrics to assess COPD severity and progression have been proposed (e.g., quality of life, BODE index), decline in FEV_1 remains a clinically and epidemiologically relevant measure. To address this important question, future studies will require the following: (*1*) improved phenotyping of subjects with COPD to assess COPD subtypes; (*2*) improved phenotyping of COPD exacerbations, with frequent assessments to limit recall bias; (*3*) large sample sizes with a broad spectrum of COPD severity and increased representation of women; and (*4*) careful longitudinal follow-up and statistical analysis.

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