Published in final edited form as:

Curr Opin Pulm Med. 2019 March ; 25(2): 132–137. doi:10.1097/MCP.0000000000000553.

Initiating drug therapy in early-stage COPD: does it impact the course and outcome?

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Abstract

Purpose of review: Early chronic obstructive pulmonary disease (COPD) is emerging in importance for the clinical and research settings. This review will highlight a proposed definition of early COPD, examine early and midlife factors that lead to development of early COPD, and review the literature pertaining to the treatment of mild COPD to gain insight into potential therapeutic approaches for early disease.

Recent Findings: Definition and Significance of early COPD: Early COPD can be defined as disease occurring in patients younger than 50 years in age with a 10-pack-year or more smoking history and abnormal spirometry, imaging, or lung function decline. Childhood exposures (maternal smoking, recurrent respiratory infections), childhood and adult asthma, and smoking affect middle-age lung function.

Therapeutic Studies of Mild COPD Treatments: Multiple studies of long acting muscarinic antagonists (LAMAs) in mild COPD have shown improvements in lung function and symptoms scores. Smoking cessation also has a beneficial effect on longitudinal lung function.

Conclusion: Early COPD is an important manifestation of COPD, with a newly proposed definition and associated risk factors identified. Inferring from studies on mild COPD cohorts, LAMAs and smoking cessation may have a positive effect on longitudinal lung function and symptomatic improvement.

Keywords

COPD; pathophysiology; smoking cessation; inhaled therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, progressive, but treatable disease characterized by irreversible airflow limitation caused by exposure to tobacco smoke or other noxious inhaled agents.(1) Large cohort studies describe COPD incidence rates to be the highest in the 7th and 8th decade of life, with about 20% of smokers

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Conflicts of Interest: MBD has served as a consultant for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, and Parion Sciences. RMB is supported through a grant from the National Institutes of Health.

developing COPD.(2) There is an increased recognition of a subset of younger persons who are at risk for developing COPD, described as “early” COPD.(3) These patients represent current and former smokers who manifest COPD at a respectively young age due to several risk factors including lung growth reduction, differential exposure profiles, childhood respiratory conditions including asthma, or genetic predisposition, among others factors. Variable lung function and rate of decline in forced-expiratory-volume-in-1-second (FEV1) in middle aged smokers may represent an interaction between the aforementioned risk factors and pathophysiologic response to cigarette smoke.(4) In this review, we will discuss the definition of “early” versus “mild” COPD, highlight studies that show an association between clinical and demographic factors and low lung function in middle age, review implications of current COPD screening recommendations as these pertain to identification of early COPD, and review the few trials in mild COPD investigating inhaled therapy and life style modification on COPD outcomes.

The Definition and Significance of Early COPD

“Early” COPD is emerging as a concerning phenotype of COPD for practitioners and researchers due to the affected demographic, perceived rapid and early decline in lung function, and current lack of definitive and targeted therapeutic approaches to-date. A clear definition of “early” COPD is imperative. Previous reviews have discussed the multifactorial and heterogeneous nature of this condition.(5, 6) Martinez *et al.*(5) propose a definition of “early” COPD as disease occurring in patients younger than 50 years old with a 10-pack-year-or-more smoking history who have any of spirometry-defined airway obstruction, CT scan abnormalities congruent with chronic smoking-related airway disease (signs of emphysema or chronic bronchitis), or a decline in FEV1 ≥ 60 ml/yr out of proportion to fall in FVC irrespective of pulmonary symptoms. This definition differs from mild COPD, a phenotype seen in older individuals with mild obstructive abnormalities. While these criteria require further validation and exist for the development of studies directed at this cohort of COPD patients, it can be surmised that patients with similar signs and histories present to primary care providers and pulmonologists not infrequently, and understanding what therapies may be most helpful in an early COPD phenotype is important as we await more definitive study results.

Tantamount to recognizing and treating those with early COPD, is understanding the risk factors that lead to its development. Early COPD may reflect either accelerated lung function loss from maximally developed lungs or failure to reach maximal lung growth with or without accelerated lung function loss (Figure 1).(6) Several recent publications highlight the importance of early life events on subsequent lung function. Early childhood respiratory infections and early-life home overcrowding are associated with decreased midlife lung function in smokers.(7) An analysis of 2438 participants examined trajectories of lung function decline from the age of seven to 53, finding 4% of the cohort met criteria for an “accelerated decline” phenotype.(8) The accelerated decline phenotype, along with participants with persistently low and below-average lung function, had a higher risk of COPD at 53 years. Childhood respiratory infections, bronchitis, asthma, and maternal smoking were associated with the accelerated decline, persistently low lung function, and persistently below-average lung function phenotypes. Personal smoking and adult asthma

were specifically associated with the accelerated decline phenotype. Additional studies have corroborated these findings suggesting a combination of childhood asthma symptoms, reduced childhood FEV1, and active asthma in young and middle adulthood are associated with the presence of COPD in middle age. (9–11) Radiographic small airway disease has also been associated with more rapid FEV1 decline(12), suggesting small airway damage from the abovementioned risk factors may be present on cross-sectional imaging. Other imaging findings, such as altered parent-to-child airway ratios, may be associated with rapid lung function decline, as well.(13) The identification of genetic factors is at the forefront of understanding propensity for the development of early COPD. However, current studies have not yet identified a specific genetic phenotype that significantly segregates to those more likely to develop early COPD.(14) These recent studies highlight the growing body of evidence leading to improved understanding of the pathophysiology of early COPD.

The issues surrounding the identification of early COPD remains challenging for the clinician encountering these patients in practice. Both the United States Preventative Services Task Force and Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) treatment strategy document recommend screening spirometry only for those with COPD risk factors and symptoms, while recommending against screening asymptomatic smokers for COPD.(1, 15) While this approach is prudent in everyday practice, it requires vigilant symptom assessment which may not occur in younger patients outside the typical COPD demographic. Further, process-of-care studies suggest improper spirometry utilization and interpretation may be prevalent in primary care practices.(16, 17) Continuing to elucidate the clinically-relevant risk factors for development of early COPD can provide direction as to which asymptomatic patients could potentially benefit from spirometry testing to identify early COPD. The studies outlined previously may aid in aggressive case finding, and recent studies examining the effect of interventions targeted to those who have mild disease could provide insight into initial treatment approach.

Therapeutic Studies of Mild COPD Treatment

Currently available trial data is focused on the treatment of mild, rather than early, COPD. No investigations currently study cohorts comprised entirely of individuals who would be defined as having early COPD. However, analysis of studies focused on mild COPD may provide insight into the effect of initiation of inhaled therapies early in the disease course. An important historical reference is the Lung Health Study(18) which assessed the response to smoking cessation with 36 mcg of inhaled ipratropium thrice daily, smoking cessation to inhaled placebo, and usual care. The mean age of the treatment arm was 48.4 years (SD 6.8) and mean FEV1 % predicted was 75.1 (SD 8.8), representing a study population largely of early COPD. The smoking cessation and ipratropium arm in this study had an initial 39 ml increase in post-bronchodilator FEV1 at one year follow up compared to a 11 ml increase in the smoking cessation and placebo group ($p<0.05$). However, after the first year of this 5-year study, FEV1 declined at the same rate in both groups. Further, the effect of ipratropium was not seen to cause a durable effect when ipratropium was stopped at the end of the trial. Sustained smoking cessation significantly decrease the rate of lung function decline in this cohort largely meeting the Martinez *et al* criteria for early COPD.

The UPLIFT trial examined the impact of tiotropium on COPD outcomes.(19) A *post hoc* analysis of UPLIFT examined the effect of tiotropium among those with mild COPD. (20) An older cohort of 632 participants (mean age 64) with FEV1 60% predicted was compared to 578 controls with similar lung function. There was no difference between mean post-bronchodilator FEV1 rate of decline in those given tiotropium versus controls (41ml/yr vs 49ml/yr, respectively, $p=0.07$). However, the tiotropium treated group showed several key findings: 1) significant improvement in pre- and post-bronchodilator FEV1 when compared to controls at every six month interval over the course of four years ($p<0.0002$ at each time interval); 2) greater proportion of participants with a SGQR score improvement 4 (52% vs. 44% of controls, $p<0.05$); and 3) 17% reduction in risk for exacerbation over the four-year trial period (HR=0.83, $p=0.011$).(20) This study offers insight into the potential salutary benefits of LAMA in mild COPD, but cannot be directly extrapolated to early COPD.

More recent prospective studies have attempted to elucidate the role of tiotropium in treatment of mild COPD. Kato *et al* (21) performed a 40-participant crossover study in a cohort with heart failure, reduced ejection fraction, and a mean FEV1 % predicted of 77.9% (SD 5.4). While the main aim of this study was to demonstrate the improvement in brain natriuretic peptide and left ventricular ejection fraction after 28 days of tiotropium treatment, there was also a significant increase in FEV1 with tiotropium (150–180 ml FEV1 improvement in crossover groups; $p<0.001$ for both groups).(21) The two crossover groups also demonstrated a statistically significant increase in 6-minute walk test (19 and 23 meters; $p<0.001$) while receiving tiotropium. Both FEV1 and 6-minute walk distance returned to near baseline at 28 days in the crossover group that had tiotropium withdrawn.

Among those with reduced FEV1 at young age, continued smoking negatively impacts subsequent lung function.(7, 8) Two studies describe the short-term impact of smoking cessation and muscarinic antagonists on pulmonary outcomes in mild COPD. Analyzing a subset of participants from the original Lung Health Study(18), Li *et al* (22) sought to determine the effect of smoking cessation and sex differences with scheduled thrice-daily ipratropium versus placebo on those with mild-to-moderate COPD. The mean FEV1 was 75% predicted and mean age was 48 years in this investigation. After 4 months of treatment, those randomized to ipratropium had a 100 ml increase in FEV1 from baseline versus 90 ml loss in the placebo group ($p<0.001$). Further, women were more likely than men to have an increase in post-bronchodilator FEV1 greater than 140 ml at 4 months (44% of women vs. 37% of men), suggesting that females with mild COPD may respond more robustly to ipratropium use. Pezzuto *et al* (23) compared COPD outcomes at three months 200 mild COPD patients treated with glycopyrronium, of whom 120 successfully quit smoking with varenicline and 80 who were unsuccessful at smoking cessation with varenicline. Participants in this study were ~42 years old with FEV1 ~76% predicted. At three months, those who quit smoking had a significantly increased FEV1 (90.4% predicted vs. 80.3% predicted for non-quitters, $p<0.01$), improved CAT (10.5 vs. 15.5 for non-quitters, $p<0.01$) and mMRC (1 vs. 1.5 for non-quitters, $p<0.01$), but did not have improved performance on a 6-minute walk test in univariate analysis. This study used parsimonious modeling to determine clinical outcomes significantly improved at three months in those who had quit smoking in multivariate modeling and found none. Pezzuto *et al* (23) and Li *et al* (22) show short-term improvements in FEV1 in young cohorts, with Pezzuto *et al* (23) further

illustrating improved lung function in those treated with a LAMA who successfully quit smoking.

The most rigorous investigation of the role of tiotropium in early stage COPD was the Tie-COPD study conducted by Zhou *et al.*(24) This study recruited GOLD stage 1 or 2 (FEV1>50% predicted) COPD patients from 24 centers in mainland China. Participants were randomized in double-blinded fashion to two-years of 18 mcg tiotropium versus placebo (n=383/group), with the primary endpoint of between-group difference in change from baseline to two-year pre-bronchodilator FEV1. Multiple secondary endpoints were assessed including between-group difference in post-bronchodilator FEV1 at 24 months, rate of annual FEV1 decline, symptom burden, and exacerbation outcomes. The majority of participants were male, with 21% having never smoked, 41% currently smoking, and 73% with minimal symptoms (defined as COPD Assessment Test (CAT) score <10). At 24 months, the pre-bronchodilator FEV was 157 ml higher in the treatment arm (p<0.001). There was no difference (p<0.06) between the rate of decline in the treatment group (38 ml/yr) and placebo group (53 ml/yr). Conversely, the post-bronchodilator rate of decline was 29 ml/yr in the treatment group and 51 ml/yr in the placebo group (p=0.006). Those in the treatment group showed more favorable exacerbation rates, including a lower frequency of all exacerbations (0.27 vs. 0.50 events per patient year, p<0.001) and hospitalizations for COPD exacerbations (0.03 vs. 0.07 per patient year, p=0.009). The treatment group also had more favorable COPD symptom scores across study visits. There was no difference in adverse events among the two groups.

There are several important conclusions to be drawn from the Tie-COPD study. Although there were fewer participants with exacerbations in Tie-COPD compared to the subgroup of moderate COPD from the UPLIFT trial (25), the beneficial reduction in exacerbation risk with tiotropium observed with Tie-COPD exceeded that seen in UPLIFT. The benefit of tiotropium on lung function and exacerbation rates in mild COPD with minimal or no symptoms was promising, but not conclusive as these findings were from subgroup analyses. Rates of FEV1 decline were similar between the two groups at 6 months, and medication-free follow-up showed similar pulmonary function between the two groups after one year, calling into question the disease modifying effect of tiotropium. The Tie-COPD study highlights the need for additional large scale, long-term studies on those with mild COPD and early COPD phenotypes

Conclusion

Early COPD is of growing importance, and tools to assist in accurate detection and appropriate initiation of therapy are needed. Parameters to define early COPD have been outlined and should be validated. Moreover, specific therapeutic trials focusing on an early COPD cohort are needed. Several recent studies have examined the risk factors associated with the development of reduced lung function in the middle age. While we await focused studies in those with early COPD, we are left extrapolating from investigations in those with milder COPD. Some of the recent investigations did enroll a younger cohort, and may be considered a proxy for an early COPD cohort. With the currently available data, a

conclusion as to whether the disease state of early COPD can be modified with drug therapy cannot be answered. Despite this, we would like to highlight the following:

- Early COPD is one of the many manifestations of COPD, with a recently proposed definition as a person who is less than 50 years-old, with greater than 10 pack-year smoking history, and one or more of either 1) spirometric airways obstruction, 2) radiographic findings suggestive of chronic airway disease, or 3) decline in lung function ≥ 60 ml/year.
- Several factors contribute to decreased lung function at an early age, including low birth weight, early childhood personal and passive tobacco smoke exposure, childhood asthma, maternal smoking, failure to reach maximal lung capacity, and active adult smoking.
- Early risk factor identification and modification is a rich target for future intervention to slow disease course in early COPD or to prevent this entity altogether.
- Studies in mild COPD suggest that treatment with muscarinic antagonists, coupled with sustained smoking cessation, improve COPD outcomes and may prove beneficial in early COPD.

To date, no societies have produced guidelines on the entity of early COPD. As more studies become available on this subset of COPD patients, it is likely the approach to their therapy will become more refined. In the interim, we suggest that those with early COPD can be identified by a thorough history and spirometry testing, and that inhaled muscarinic antagonists and smoking cessation may prove beneficial to slow the progression of disease and improve patient health status.

Acknowledgements:

Financial Support and Sponsorship: RMB is supported by grant 1F32HL143867-01 (NIH-NHLBI).

Disclosure of Funding: There was no specific funding to support this manuscript.

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Key Points

- Current definitions for early COPD have been proposed, but need further validation.
- Poorer middle age lung function is due to identifiable childhood and adult risk factors including maternal smoking, low birth weight, childhood and adult asthma, and smoking.
- Aggressive case finding for early COPD includes risk factor and symptom assessment, followed by spirometry testing.
- No therapeutic trials are directed at those with early COPD, but evidence is present for those with mild, late-onset COPD.
- A combination of sustained smoking cessation and muscarinic antagonists improve lung function, exacerbation rates, and symptom measures in mild COPD patients. Results that may be able to be extrapolated to those with early COPD.

Figure 1.

Mechanisms of development of early COPD. (A) Normal lung function natural history. (B) Reduced lung growth during fetal development, childhood, or adolescence (which might be independent), any of which can reduce attained lung function. (C) Shortened plateau. (D) Accelerated lung function loss during adulthood. (E) Episodic loss of lung function without full recovery. (F) Late accelerated loss of lung function. FEV₁=forced expiratory volume in 1 s. *Presence of early disease for each disease natural history. (Reproduced with permission from Rennard SI and Drummond MB. *Lancet*. 2015 May 2;385(9979):1778–1788.).