Rate of Decline of FEV_1 as a Biomarker of Survival?

For decades, the natural history of chronic obstructive pulmonary disease (COPD) has been defined by the excess decline in lung function induced by tobacco smoking, with FEV_1 considered the gold standard biomarker of COPD development and progression (1). Several studies have been conducted to assess the effect of smoking cessation (2) and/or pharmacological treatment on FEV_1 decline with the primary aim of identifying treatments that could reduce lung function decline and thus disease progression, potentially improving survival. Unfortunately, no study with FEV_1 decline as primary outcome has proven an effect of pharmacological treatment on lung function decline (3). Even in the Lung Health Study, which showed a positive effect of smoking cessation, there was no effect from ipratropium (2).

We now understand the several limitations of those studies. First, patients have been studied for a relatively short period of time (maximum 4 yr). Second, patients were typically studied late in life, when the decline slows down. Third, and more importantly, we now know that only 50% of patients who present with COPD after the age of 50 years attained high maximal lung function in their twenties and then underwent fast decline, the rest having attained low maximal lung function because of early events and who therefore developed COPD without excess decline (3, 4). The fact that these two routes are indistinguishable later in life, at the age of 50–60 years when the diagnosis of COPD is usually established, prevents the identification of the fast decliners.

Subsequent studies were performed with other primary outcomes, such as survival in TORCH (TOwards a Revolution in COPD Health) (5) and SUMMIT (Study to Understand Mortality and Morbidity in COPD) (6), with lung function decline assessed as a secondary outcome. More recently, exacerbations have been increasingly used as primary outcome, particularly in phase 3 studies such as IMPACT (Informing the Pathway of COPD Treatment) (7) and ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) (8), which were the first studies to show an effect of pharmacological treatment on survival, although not as primary outcome.

Because *post hoc* analyses of some pharmacological studies had shown a positive effect on FEV_1 decline, either as a secondary outcome or in subgroups of patients with COPD (6, 9, 10), in this issue of the *Journal*, Celli and colleagues (pp. 689–698) decided to undertake a careful systematic review of placebo-controlled pharmacological trials lasting longer than 1 year to answer the question of whether FEV_1 decline can indeed be ameliorated by therapy (11). They observed an average difference in FEV_1 decline of 5 ml per year between active medications and placebo and suggested that it corresponds to the benefit reported for clinically relevant outcomes (such as health status and exacerbation rates) that are considered to be improved by the same agents in the same studies. They concluded that pharmacotherapy is effective in altering the rate of lung function decline and that because the yearly absolute difference observed was similar to the treatment difference reported for clinical outcomes, current guidelines should be adjusted to reflect these findings, and future studies should include the effects on lung function decline, particularly in patients with rapid lung function decline. We agree with the authors' conclusion on the importance of the overall positive effect of long-term pharmacologic treatment on lung function decline and support their suggestion that Global Initiative for Chronic Obstructive Lung Disease should reconsider this outcome in the assessment of response of COPD to treatment.

However, when considering the strength of this proposal, as nicely discussed by the authors, the difference versus placebo of 5–9 ml/yr is most likely too small to be used as an outcome not only in studies comparing active treatment against an active comparator but also in individual patients. By contrast, this difference may become identifiable (especially in fast decliners) if spirometry is performed in smokers from early in life (e.g., at 20–30 years of age) and at regular intervals afterward (4, 10, 12). Interestingly, as very elegantly recently reported by Marott and colleagues (12), fast decliners *1*) may indeed be identified in long-term follow-up (60 ml/yr vs. 30 ml/yr) and *2*) are at increased risk of death, particularly respiratory death possibly owing to continuing smoking. The simplified model of lung function decline (normal and COPD slow or fast decliners) in that study is illustrated in Figure 1. This model could provide the framework for future studies aimed to prevent excessive lung function decline and its respiratory and systemic consequences in fast decliners.

Regular measurement of lung function with simple spirometry including FVC would also allow an assessment of the relative value of FEV_1 and FVC as biomarkers of COPD progression and/or survival.

The mechanisms of airflow limitation and excess decline are rather complex and may involve not only smooth muscle contraction, hypersecretion, and airway wall remodeling but also destruction of small airways and emphysema and systemic extrapulmonary effects (13). Thus, exploring the potential effects of pharmacological treatment on airflow limitation and decline in lung function should not be limited to long-acting bronchodilators and inhaled corticosteroids but possibly to other antiinflammatory (13, 14) and antifibrotic agents (15). In this context, lung diseases previously believed to be irreversible, such as idiopathic pulmonary fibrosis, have been shown to be sensitive to antifibrotic agents such as nintedanib and pirfenidone, both of which are effective in preventing lung function decline in patients with idiopathic pulmonary fibrosis (15). These agents might be effective in reducing lung function decline in patients with COPD dominated by airway wall remodeling. Finally, because lung function decline might reflect systemic effects of

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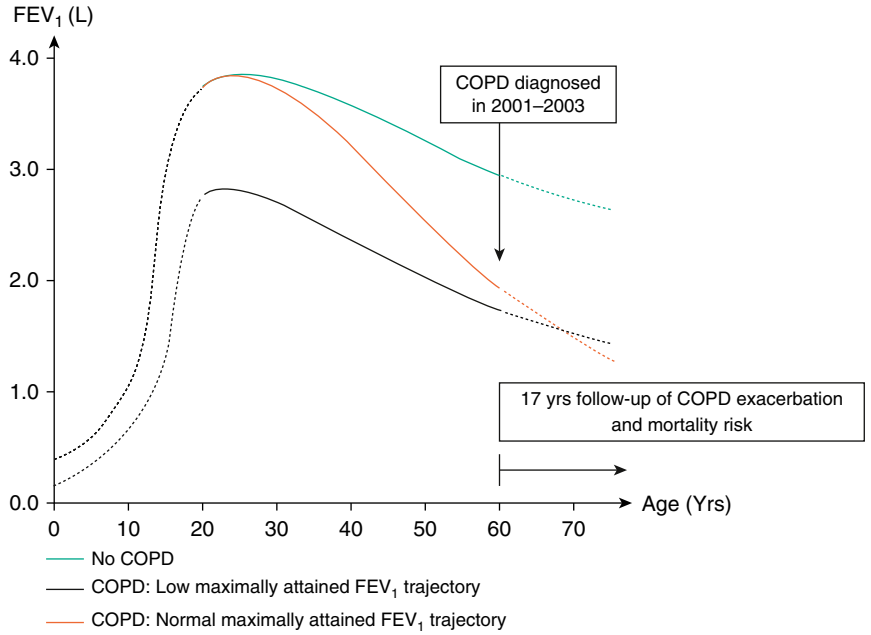

Figure 1. Outline of the study. Participants were assigned into one of three FEV_1 trajectories of interest: no chronic obstructive pulmonary disease (COPD), COPD developed through low maximally attained FEV_1 trajectory, and COPD developed through normal maximally attained FEV_1 trajectory based on information from the 1976–1978 or 1981–1983 examination. After the baseline 2001–2003 examination, individuals were followed for 17 years with regard to risk of severe exacerbations of COPD, repiratory disease mortality, and all-cause mortality. Reprinted by permission from Reference 12.

smoking, agents used for the treatment of frequent cardiovascular comorbidities of COPD might also be tested (3), or biologics that markedly improve lung function in severe asthma with airflow limitation (16), with the aim to verify whether comprehensive treatment of patients with COPD and one or more comorbidity might reduce lung function decline taken as a biomarker of survival. ■

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References

1. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645–1648.
2. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, *et al*. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. *JAMA* 1994;272:1497–1505.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2021 [accessed 2020 Dec 10]. Available from: https://goldcopd.org/2021-gold-reports/.
4. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019;7:358–364.
5. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, *et al*.; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
6. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, *et al*.; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817–1826.
7. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al*.; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with copd. *N Engl J Med* 2018;378: 1671–1680.
8. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, *et al*.; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe copd. *N Engl J Med* 2020;383: 35–48.
9. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, *et al*. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178:332–338.
10. Morice AH, Celli B, Kesten S, Lystig T, Tashkin D, Decramer M. COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT). *Respir Med* 2010;104:1659–1667.
11. Celli BR, Anderson JA, Cowans NJ, Crim C, Hartley BF, Martinez FJ, *et al*. Pharmacotherapy and lung function decline in patients with chronic obstructive pulmonary disease: a systematic review. *Am J Respir Crit Care Med* 2021;203:689–698.

12. Marott JL, Ingebrigtsen TS, Çolak Y, Vestbo J, Lange P. Lung function trajectories leading to chronic obstructive pulmonary disease as predictors of exacerbations and mortality. *Am J Respir Crit Care Med* 2020;202:210–218.
13. Gladysheva ES, Malhotra A, Owens RL. Influencing the decline of lung function in COPD: use of pharmacotherapy. *Int J Chron Obstruct Pulmon Dis* 2010;5:153–164.
14. Lo Bello F, Hansbro PM, Donovan C, Coppolino I, Mumby S, Adcock IM, *et al*. New drugs under development for COPD. *Expert Opin Emerg Drugs* 2020;25:419–431.
15. Raghu G, Selman M. Nintedanib and pirfenidone: new antifibrotic treatments indicated for idiopathic pulmonary fibrosis offer hopes and raises questions. *Am J Respir Crit Care Med* 2015;191:252–254.
16. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med* 2019;199:433–445.

Biological Mechanisms of Cognitive and Physical Impairments after Critical Care

Rethinking the Inflammatory Model?

There is a growing population of critical illness survivors who experience persistent impairments in physical, cognitive, and mental health outcomes. When assessed using detailed cognitive test batteries, almost two-thirds of survivors have substantial cognitive impairment at 12-month follow-up (1). Muscle weakness is also common and persistent after an ICU stay and is associated with impairment in physical functioning and health-related quality of life (2, 3).

Studies have identified clinical risk factors associated with these persistent impairments, but few large-scale studies have evaluated biological mechanisms (Figure 1) (1, 3). In preclinical studies, acute inflammatory biomarkers are associated with persistent cognitive impairment (4, 5) and muscle weakness (6). In critically ill patients, systemic inflammation has been associated with muscle weakness (7). Little is known, however, about the association between acute inflammatory responses and postdischarge cognitive and physical impairments (8). In this issue of the *Journal*, Brummel and colleagues (pp. 699–706) make an important contribution to the literature by evaluating the association between inflammatory and coagulation protein biomarkers with impairments in cognition and physical functioning at 3- and 12-month follow-up (9).

This study evaluates patients enrolled, from 2007 to 2010, into one of two multicenter, prospective cohort studies conducted at medical and surgical ICUs at five academic, community, and Veterans Affairs hospitals (9). The most common admission diagnostic categories of enrolled patients were sepsis (30%), surgical procedure (18%), cardiac (17%), and acute respiratory failure (16%), with a median (interquartile range) mechanical ventilation duration of 2 (1–6) days (9). Patients with preexisting cognitive impairment were excluded, and statistical analyses were adjusted for baseline physical function status, evaluated via survey-based measures. The following plasma biomarkers were quantified on Days 1, 3, and 5: CRP (C-reactive protein), IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, MMP-9 (matrix metalloproteinase-9), TNF-α (tumor necrosis factor α), soluble tumor necrosis factor receptor 1, and protein C. Separate regression models were used to evaluate the association between each biomarker and the following four outcome measures evaluated at 3 and 12 months: Repeatable Battery for the Assessment of Neuropsychological Status and Trail Making Test-Part B for cognition, and Katz Activities of Daily Living (ADL) Index and Functional Activities Questionnaire assessment of Instrumental ADL for physical function.

Of 630 survivors at 3-month follow-up, approximately 400–500 had full or partial outcome assessments at the 3- and 12-month time points. At both time points, cognitive test scores were approximately 1 SD below age-adjusted population means, and approximately one-fourth of survivors had physical disability. Notably, there was no association between any biomarker and cognitive test scores, but at both time points, higher levels of CRP and MMP-9 were associated with worse ADL and Instrumental ADL scores.

The study is notable for its large sample size with broad representation of ICU patients, and longitudinal capture of biomarkers early during critical illness. Furthermore, the measured biomarkers comprehensively evaluated dysfunctional inflammatory pathways that have been associated with adverse clinical outcomes in acute respiratory distress syndrome (ARDS) and sepsis. Moreover, statistical methods were used to help address potential bias from missing or incomplete outcome assessments.

Findings from this study suggest several areas for future research. First, the biomarkers in this population were only modestly elevated compared with more recent studies in patients with ARDS and sepsis (10). Hence, future studies should further refine patient eligibility criteria to select for those who may have a more robust inflammatory response. In addition, studies should further evaluate the association of CRP and MMP-9 with post-ICU physical outcomes because it was not possible to ascertain whether these markers have a specific mechanistic role or are merely a marker of disease severity, as the authors noted (9). The latter might manifest as an increased duration of mechanical ventilation and sedation, which may be associated with worse outcomes, independent of systemic inflammation. The duration of mechanical ventilation and the incidences of ARDS and sepsis were low in this study; therefore, some important risk factors for impairments may not have been fully captured.

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