REVIEW

Lung function decline in COPD

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Abstract: The landmark study of Fletcher and Peto on the natural history of tobacco smoke-related chronic airflow obstruction suggested that decline in the forced expiratory volume in the first second (FEV_1) in chronic obstructive pulmonary disease (COPD) is slow at the beginning, becoming faster with more advanced disease. The present authors reviewed spirometric data of COPD patients included in the placebo arms of recent clinical trials to assess the lung function decline of each stage, defined according to the severity of airflow obstruction as proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. In large COPD populations the mean rate of FEV_1 decline in GOLD stages II and III is between 47 and 79 mL/year and 56 and 59 mL/year, respectively, and lower than 35 mL/year in GOLD stage IV. Few data on FEV_1 decline are available for GOLD stage I. Hence, the loss of lung function, assessed as expiratory airflow reduction, seems more accelerated and therefore more relevant in the initial phases of COPD. To have an impact on the natural history of COPD, it is logical to look at the effects of treatment in the earlier stages.

Keywords: chronic obstructive pulmonary disease, decline, forced expiratory volume in 1 second, FEV_1

Introduction

Assumptions about lung function decline occurring in chronic obstructive pulmonary disease (COPD) have been greatly influenced by the landmark study of Fletcher and Peto[1] on the natural history of tobacco smoke–related chronic airflow obstruction.[2] More than 30 years ago, Fletcher and Peto[1] measured the forced expiratory volume in 1 second (FEV_1) every 6 months for an 8-year follow-up period in a cohort of 792 working men, drawing the well-known graph of FEV_1 decline over time in COPD (Figure 1). FEV_1 was originally expressed as a percentage of the value calculated by extrapolation back to the age of 25 years, made equal to 100, and time in years from age 25 to age 75.

A lot of information arose from Fletcher and Peto's[1] pioneering work: the individual susceptibility to smoking-related lung functional damage, the unavoidable progression of the airflow obstruction once COPD is established, the large variability of the abnormal lung function decline among different subjects, the possible reduction of the excessive FEV_1 decline after smoking cessation at all times, and the paucity of self-reported symptoms when the airflow reduction is mild to moderate. However, among the various messages offered by their analysis, the most retained was that the rate of FEV_1 decline increased progressively with time in susceptible smokers. In other words, in the COPD

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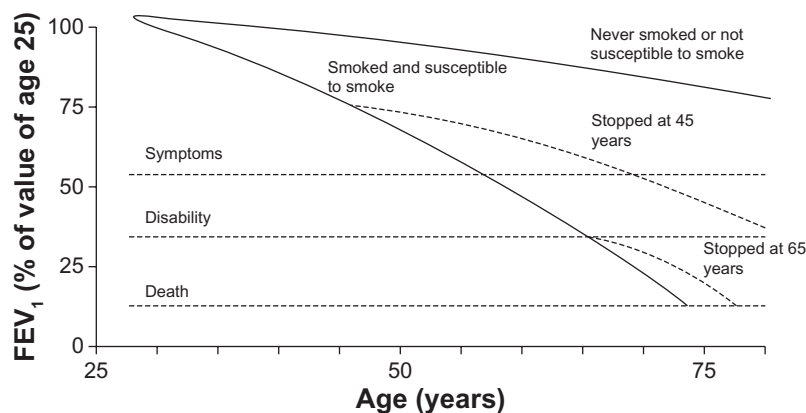Fax +39 030 39 80 69
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Figure 1 Modified version of Fletcher and Peto's[1] graph showing the decline in the forced expiratory volume in the first second (FEV$_1$).

patients who smoked, the lower the FEV$_1$, the greater its subsequent decline for similar intervals of time.

Some limitations must be acknowledged in the work of Fletcher and Peto.[1] All subjects were male, their recruitment age was between 30 and 59 years only, and the follow-up period was relatively short compared with the large time range shown on the x-axis of Fletcher and Peto's[1] graph (Figure 1). Therefore, the curves shown in the graph were largely extrapolated backward and forward with inherent inaccuracies, possibly leading to an erroneous picture of the phenomenon. Because of this, the present authors believe that a false idea of lung function decline in COPD has been inculcated in pulmonologists, suggesting that the disease progresses slowly at the beginning and that the loss of function markedly increases only when a given degree of severity has been reached. As a consequence, major therapeutic efforts have been focused on severe to very severe airflow obstruction in COPD patients. Recently, large amounts of data have been collected to challenge Fletcher and Peto's[1] hypothesis.

In the framework of the classification of airflow obstruction severity proposed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[3] the authors analyzed the spirometric data of COPD patients enrolled in recent prospective clinical trials and randomized in the placebo arms to assess the natural rate of FEV$_1$ decline of each stage.

Methods

The authors searched the PubMed database and collected the data available after 1990 on the average rate of FEV$_1$ decline found in large observational studies and in recently published prospective randomized control trials on COPD patients and measured in the respective placebo arms with a follow-up of at least 3 years.

Results

The most important data concerning the average rate of FEV$_1$ decline prospectively measured in large COPD cohorts are shown in Table 1.

Only one large study was found about COPD patients with FEV$_1$ higher than 80% of the predicted value (GOLD stage I). A total of 430 COPD patients recruited in the first stage of the Swiss Study on Air Pollution and Lung Diseases in Adults exhibited an average annual decline in FEV$_1$ of about 40 mL/year over 11 years.[4] Within this cohort, the subgroup of asymptomatic patients had a slightly slower decline than those with chronic cough and phlegm.[4] A much smaller cohort of GOLD stage I and II COPD patients was followed for 3 years in the Copenhagen City Heart Study,[5] and this cohort showed a similar annual reduction in FEV$_1$. Further studies are urgently needed to establish firmly how FEV$_1$ declines in GOLD stage I COPD patients. Data collected on COPD patients recruited in GOLD stage II (with FEV$_1$ between 79% and 50% of the predicted value) by Anthonisen et al (for the Lung Health Study [LHS]),[6] Pauwels et al,[7] Anthonisen et al (for the LHS-3),[8] the LHS Research Group,[9] and Jenkins et al[10] are consistent, reporting a mean annual FEV$_1$ decline of 56, 69, 53, 47, and 60 mL/year, respectively. However, it should be noted that in the post hoc analysis from the TORCH (TOwards a Revolution in COPD Health) study the placebo group did not faithfully represent the whole of GOLD stage II, because the inclusion criteria required a pre-bronchodilator FEV$_1$ value of less than 60% of the predicted value.[10] Accordingly, the COPD patients included in this placebo group had a baseline pre-bronchodilator FEV$_1$ between 60% and 50% of the predicted value. Recently published data in the Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease (GLUCOLD) study showed a decline in the placebo group greater than

Table 1 Rate of annual decline in the forced expiratory volume in the first second (FEV_1) recorded in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I–IV chronic obstructive pulmonary disease patients randomized in the control arm during longitudinal studies with a follow-up period of at least 3 years

Reference	Study	GOLD stage	Patients (n)	Age range (yr)	Follow-up period (yr)	Mean FEV_1 decline (mL/yr)*
Bridevaux et al[4]	SAPALDIA 1	I	430	18–60	11	40 ± 37[†]
Vestbo et al[5]	CCHS	I–II	145	59 ± 10[§]	3	42[††]
Anthonisen et al[6]	LHS	II	1964	35–60	5	56[††]
Pauwels et al[7]	EUROSCOP	II	643	30–65	3	69[††]
Anthonisen et al[8]	LHS-3	II	1357	30–60	11	53[††]
LHS Research Group[9]	LHS-2	II	557	40–69	3	47[††]
Jenkins et al[10]	TORCH	II	535	40–80	3	60[††]
Lapperre et al[11]	GLUCOLD	II	24	45–75	3	79[††]
Decramer et al[12]	UPLIFT	II	1355	64 ± 9[§]	4	49[††]
Burge et al[13]	ISOLDE	III	375	40–75	3	59[††]
Jenkins et al[10]	TORCH	III	775	40–80	3	56[††]
Decramer et al[12]	UPLIFT	III	1331	65 ± 8[§]	4	38[††]
Jenkins et al[10]	TORCH	IV	214	40–80	3	34[††]
Decramer et al[12]	UPLIFT	IV	271	63 ± 8[§]	4	23[††]

Notes: [§]Mean age plus or minus the standard deviation; *standard deviation is shown when available; [†]pre-bronchodilator FEV_1; [††]post-bronchodilator FEV_1.
Abbreviations: CCHS, Copenhagen City Heart Study; EUROSCOP, European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; GLUCOLD, Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease study; ISOLDE, Inhaled Steroids in Obstructive Lung DiseasE study; LHS, Lung Health Study; LHS-2, Lung Health Study 2; LHS-3, Lung Health Study 3; SAPALDIA 1, first stage of the Swiss Study on Air Pollution and Lung Diseases in Adults; TORCH, TOwards a Revolution in COPD Health study; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium study; yr, year.

that found in previous studies, in average amounting to 79 mL/year.[11] A secondary analysis of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study evaluated the effects of long-term treatment with tiotropium in GOLD stage II COPD patients.[12] Pre-bronchodilator FEV_1 declined by a mean of 49 mL/year in the control group. However, this group was not a true placebo group, because all respiratory medications, except other inhaled anticholinergic drugs, were allowed during the trial and about 65% of these patients in the control arm were taking two active drugs. Because of this, the lower mean FEV_1 decline in the UPLIFT control group cannot be considered as truly representative of GOLD stage II COPD. Therefore, it is reasonable to estimate that the mean post-bronchodilator FEV_1 decline of GOLD stage II COPD patients amounts to 61 ± 12 mL/year, with a little bias toward the lowest initial FEV_1 values in this stage. Lung function decline of COPD patients recruited in GOLD stage III is much better defined. In fact, Jenkins et al[10] and Burge et al[13] had very homogeneous data with a mean FEV_1 decline from 56 to 59 mL/year. Interestingly, the FEV_1 decline reported by Anzueto et al[14] in a 1-year follow-up study performed in the same stage of COPD severity amounted in the placebo arm to 58 mL/year. The average FEV_1 decline found by Decramer et al[12] in GOLD stage III in the control arm of the UPLIFT study, amounting to 38 mL/year, is likely underestimated for the same reason mentioned above. A few data available

about COPD patients recruited with FEV_1 less than 30% of the predicted value have shown a much slower mean FEV_1 decline at GOLD stage IV than at other stages.[10,12]

Dawkins et al[15] published interesting data about lung function decline in patients with alpha-1-antitrypsin deficiency-related emphysema stratified according to the GOLD guidelines (Table 2). In emphysematous COPD patients with the PiZ phenotype, the mean annual FEV_1 decline was higher in moderate disease, corresponding to GOLD stage II, and was greater than in the general COPD population. These data suggest that COPD patients suffering from panlobular emphysema have the highest rate of FEV_1 decline occurring in the early phase of the disease. This has

Table 2 Rate of annual decline of the forced expiratory volume in the first second (FEV_1) in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I–IV chronic obstructive pulmonary disease patients with alpha-1-antitrypsin deficiency-related emphysema measured during a longitudinal study with a 3-year follow-up period[15]

GOLD stage	Patients (n)	Age range (yr)[§]	Mean FEV_1* decline (mL/yr)[§]
I	18	49 ± 9	32 ± 19
II	26	51 ± 9	90 ± 19
III	38	53 ± 11	52 ± 8
IV	19	49 ± 9	8 ± 9

Notes: [§]Data are presented as mean plus or minus the standard error of the mean; *pre-bronchodilator FEV_1.
Abbreviation: yr, year.

also been reported by Vestbo et al[16] in a recently published paper on the change in FEV_1 over time in the large COPD population enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study. In this study patients with computerized tomography scan evidence of emphysema exhibited the largest rate of FEV_1 decline over a 3-year follow-up period.

Discussion

According to the evidence produced, it is clear that the loss of lung function, assessed as expiratory airflow reduction, is more accelerated and therefore more relevant in the early stages of COPD than in the late stages, with some reservation regarding GOLD stage I where consistent information is still lacking. Therefore, a different trend of the FEV_1 decline in COPD can be envisaged (Figure 2), showing an opposite view to that of Fletcher and Peto's diagram (Figure 1). This is likely because COPD patients in the early stages have more to lose than those in the most advanced stage. In addition, some of the FEV_1 loss can be partly buffered by the increase in total lung capacity in GOLD stage IV COPD patients.

Based on these findings, it seems that any attempt to positively interfere with the natural history of COPD by using different therapeutic options should logically be focused on COPD patients in at least GOLD stage II. This is suggested by the subgroup analysis of the treatment group in the GOLD stage II COPD patients of the UPLIFT study.[12] Of course,

this approach should be tested and proved by adequate randomized clinical trials.[17]

It must be acknowledged that most of the recent large COPD trials studied had a 3- to 4-year follow-up period, which is much shorter than the follow-up period in Fletcher and Peto's[1] analysis; this could be a limitation in the accuracy of the FEV_1 decline.

Furthermore, in many of these studies the percentage of dropouts was higher in the placebo arm, meaning that the average rate of FEV_1 decline of healthier COPD patients is known rather than that of the true COPD population. As a consequence, the natural rate of FEV_1 decline could be underestimated by the existing data. It is reasonable that this could be accentuated in the sicker COPD patients recruited in GOLD stage IV. However, the withdrawal from these studies is essentially because of symptoms and/or exacerbations. Since FEV_1 is poorly related to symptoms[18] and even to exacerbations,[19] it is plausible that this reasoning may similarly be applied to each COPD stage, leaving the message of a greater loss of function in the early phase of the disorder still valid.

Finally, it should be recognized that the natural history of lung function, not only in healthy never smokers and smokers but also in COPD patients, has been essentially assessed in terms of expiratory airflow reduction, looking at the FEV_1 annual change as the primary measure to track the progressive decline of lung function. This could be a limitation, especially in very sick patients.
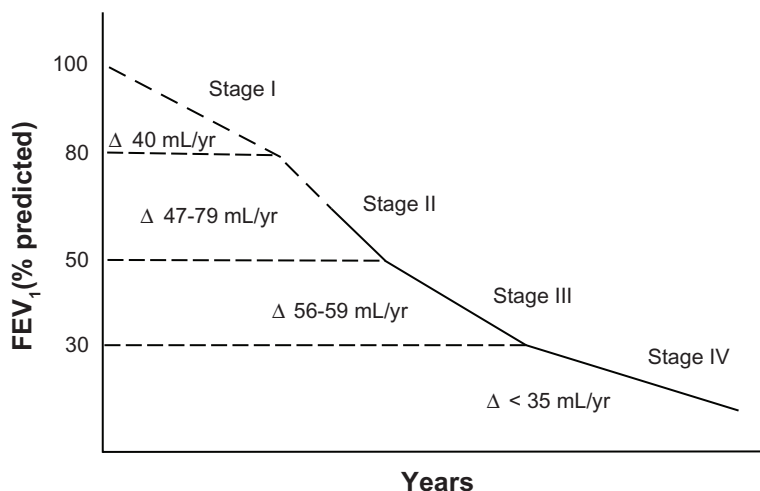

Figure 2 Range of average rate of decline in the forced expiratory volume in the first second (FEV_1) of chronic obstructive pulmonary disease patients according to initial severity of airflow reduction.
Notes: The dashed segment of the line highlights any stage or part of it where consistent information is still lacking; control data from the UPLIFT (understanding Potential Long-term Impacts on Function with Tiotropium) study were not considered in the analysis.
Abbreviation: yr, year.

Conclusion

In summary, the authors have shown that information provided in recent years about the rate of FEV$_1$ decline in COPD patients strongly supports the concept that the faster progression of functional impairment in COPD occurs early and it particularly occurs in GOLD stage II. This is in contrast with Fletcher and Peto's[1] analysis. In the present authors' view it seems more logical to make efforts for an early (spirometric) detection of COPD, based on risk factors rather than symptoms, and to plan randomized clinical trials to show the efficacy of an early strategy of intervention on the natural history of such a disorder.

Disclosure

The authors report no conflicts of interest in this work.

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