**FEV₁ decline in asymptomatic young adults: relationships with some tests of small airways function**

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**ABSTRACT:** The aim of this study is to determine whether some tests proposed as diagnostic of small airways obstruction (SAO) are useful in identifying the subjects at risk of developing chronic airflow limitation. Eighty-five healthy male workers (46 nonsmokers and 39 smokers, aged 21-41 yrs), living in the same area and not exposed to occupational pollutants were re-examined after an interval of 6 yrs. At the first survey 39 had functional evidence of SAO as determined by the presence of one of: maximal mid-expiratory flow (MMEF) <65% of predicted value (pred); maximal expiratory flow when 25% forced vital capacity remains to be expired (V_{max} \times 0.25) <60% pred; closing capacity (CC) >130% pred; 46 had all functional values in the normal range. We considered four subgroups: smokers and nonsmokers with and without SAO. The rate of decline in FEV₁, the decline in %ΔFEV₁ and ΔFEV₁-height², have been evaluated and compared in the subgroups. Initial values of specific tests (MMEF, V_{max} \times 0.25, CC and slope of phase III) have been examined for a possible relationship with decline of FEV₁. Statistical analysis of our data showed that only CC was related to FEV₁ decline. However, there were no significant differences in FEV₁ decline among the subgroups. We conclude that in young adult subjects functional characteristics of SAO have no predictive value for development of chronic airways obstruction.

**Keywords:** FEV₁, decline; longitudinal study; small airways.

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The predictive value of tests of small airways function is still controversial and the important issue to be addressed is whether these tests can be used to identify the subjects, smokers or nonsmokers, who will progress to develop irreversible airflow obstruction [1]. This question can be answered only by following a fairly large group of subjects prospectively over a period of time long enough to develop an abnormal test of large airways obstruction.

In previous studies, over a period of 8 yrs, we followed a group of 69 asymptomatic workers in an iron foundry (49 smokers and 20 nonsmokers) living in the same area [2, 3]. We found that 39% of the smokers and 15% of the nonsmokers, initially diagnosed as having peripheral airways disease, developed a more rapid fall of forced expiratory volume in one second (FEV₁) with age, indicating a progressive deterioration of ventilatory function.

**Plam et al.** [4] in a 5 yr longitudinal survey found that the changes between the first and second examination were significantly greater for steel workers than for unexposed workers, demonstrating the role of environmental pollution.

Data from longitudinal studies concerning subjects unexposed to occupational pollutants indicated an association among some abnormal tests of small airways function and an increased rate of decline of FEV₁ [5–8]. These results seemed to confirm the hypothesis that small airways may be regarded as a noisy rather than a silent zone [9]. However, the newly created clinical entity "small airways disease" was criticized from the beginning and this scepticism was strongly supported by reports concerning the reversibility of tests of small airways function on the one hand [10], and prospective epidemiological investigation on the other hand [11–13].

The aim of this longitudinal study was to determine the usefulness of some tests of small airways in identifying the subjects who are at risk of developing a chronic airflow impairment. We compared the rate of FEV₁ decline in a sample of healthy young adults, some of whom had all spirometric values in the normal range, whilst others had a functionally defined small airways obstruction (SAO).

**Methods**

Eighty-five asymptomatic male, white-collar workers, with a mean age of 35 yrs (range: 21–41 yrs), working in an atmosphere without dangerous pollutants and living in the same environment were examined. These men
were persistently totally free of respiratory symptoms or disease, with no history of heart trouble or asthma.

In order to detect the impairment of peripheral airways resistance, in the presence of normal values of FEV₁, many respiratory function tests have been suggested [14, 15]. Among these tests, closing capacity (CC) [16, 17], slope of phase III [5, 7, 8], maximal mid-expiratory flow (MMEF) [18, 19] and maximal expiratory flow at the point when 25% of forced vital capacity remains to be expired (Vmax₀.₂₅) [18, 20, 21] are easy to perform and very suitable for rapid screening of a relatively large sample of subjects.

In our study spirometric data, maximal expiratory flow volume curves and nitrogen single-breath test were measured by means of the Pulmonary Function Analyser (Hewlett-Packard, model 4740 2A). The residual volume (RV) was obtained by the separate multibreath nitrogen washout method.

The predicted values (pred) for vital capacity (VC), FEV₁, MMEF and Vmax₀.₂₅ were calculated according to the European Community for Coal and Steel standards [22]. Predicted value of CC was calculated according to Buss and Ross [23].

SAO was considered to be present at the original survey when, in the presence of FEV₁ and VC within normal limits (>80% pred), at least one or more of these tests differed from predicted value: MMEF <65% pred; Vmax₀.₂₅ <60% pred; CC >130% pred.

This definition of SAO is obviously arbitrary without the evaluation of frequency dependence of compliance, commonly considered the "gold standard" for identification of pathology in small airways [24]. We have chosen these boundaries in order to increase the specificity and the positive predictive value of the tests. All subjects had at least three satisfactory traces.

On the basis of smoking habits and of the initial values of specific tests (CC, MMEF, Vmax₀.₂₅) we divided the subjects into four categories. Group I, nonsmokers with all lung function tests within the normal range, consisted of 28 subjects. Group II consisted of 18 smokers with all tests within the normal range. Group III and group IV consisted of subjects with abnormal values of at least one among the considered tests (CC, MMEF, Vmax₀.₂₅) whereas the others were within normal limits: 18 were nonsmokers (Group III) and 21 were smokers (Group IV). Of the current smokers (39 subjects, mean age 35 yrs, range 21–41 yrs), all had had at least 6 pack-years of smoking.

Re-examination was carried out 6 yrs after the initial survey and the same procedures were applied by the same medical team as in the first survey. The smoking habit did not change during the survey. Ex-smokers were not considered in this study.

FEV₁ decline for each subject was calculated by subtracting the best FEV₁ value in the last survey from the best FEV₁ in the first. This difference was divided for the study period (in years) and expressed as ml·yr⁻¹ (A FEV₁ yr⁻¹). A linear regression for each group has been obtained plotting the individual ΔFEV₁ yr⁻¹ vs the corresponding age. The age was taken as the midpoint between the first and last spirometric test [25]. The rate of change over time for FEV₁ was calculated as the slope of the linear regression line derived from the measurements over the study period. The values of CC, slope of phase III, MMEF and Vmax₀.₂₅ at the initial visit were examined for possible relationships with change in FEV₁ decline.

Statistical analysis was carried out using Student’s t-test for paired data and Chi-squared test. The comparison of the slopes of the regression lines was carried out according to ARMITAGE [26], using regression in groups and analysis of covariance.

### Results

Age, height and lung function data (average values and standard deviation) are presented in table 1. Average results recorded 6 yrs before in the same subjects are shown in parentheses. Average age and height were comparable in the four groups. FEV₁ and VC were not statistically different among the groups. FEV₁, MMEF, and Vmax₀.₂₅ decreased (p<0.05) in all of the subjects. There were no significant changes in VC, CC and slope of phase III over 6 yrs in the four groups.

The relationships of ΔFEV₁ with age was highly significant in all groups (regression lines and equations are shown in figure 1). The reduction of FEV₁ over 6 yrs was not significantly different among the four groups: 23.34 ml·yr⁻¹ in I; 39.6 ml·yr⁻¹ in II; 35.16 ml·yr⁻¹ in III; and 38.61 ml·yr⁻¹ in IV.

#### Table 1. General characteristics and lung function data of the four groups studied

| Group | Age (yr) | Height (cm) | VC (l) | FEV₁ (l) | MMEF (l/s) | Vmax₀.₂₅ (l/s) | CC/TLC | ΔN₂⁻¹
|-------|----------|-------------|--------|----------|-------------|--------------|--------|-------
| I     | 40±7.9   | 168±7.5     | 4.7±0.77 | 3.7±0.55 | 4.2±1.04   | 1.9±0.73     | 36±5.2 | 1.64±1.1 |
|       | 33(4)    | 168(168)    | 5.1±0.76 | 3.8±0.53 | 3.7±0.86   | 1.6±0.54     | 34(1)  | 1.51±1.0 |
| II    | 42±4.7   | 171±1±1     | 5.1±0.76 | 4.1±0.88 | 4.2±0.80   | 1.5±0.59     | 40±8.6 | 1.92±1.3 |
|       | (36)     | (170)       | (5.12)  | (4.52)   | (3.24)     | (1.83)       | (36)   | (1.74) |
| III   | 42±8.6   | 166±7.9     | 4.4±0.88 | 3.3±0.68 | 2.9±0.80   | 1.5±0.59     | 41±8.2 | 4.3±2.7 |
|       | (35)     | (167)       | (4.52)  | (3.48)   | (3.24)     | (1.83)       | (35)   | (4.14) |
| IV    | 41±8.2   | 170±6.1     | 4.6±0.87 | 3.4±0.63 | 3.1±1.02   | 1.4±0.57     | 38.61  | 2.0±1.2 |

### Notes:

* p<0.05 (by two-sided paired t-test for differences in values recorded in the two surveys); §: average results recorded 6 yrs before in the same subjects are shown in parentheses; VC: vital capacity; FEV₁: forced expiratory volume in one second; MMEF: maximum mid-expiratory flow; Vmax₀.₂₅: maximal expiratory flow when 25% forced vital capacity remains to be expired; CC %TLC: closing capacity as percentage of total lung capacity; ΔN₂⁻¹: slope of phase III. Results are expressed as mean±sd.
FEV<sub>1</sub> decline in healthy subjects

A greater than 70 ml·yr<sup>-1</sup> decline of FEV<sub>1</sub> (arbitrarily chosen according to STANESCU et al. [12]) was observed in only 1 of 28 subjects in group I (3.5%); in 5 of 18 subjects in group II (28%); 4 of 18 subjects in group III (22%); and 4 of 21 subjects in group IV (19%). (Chi-squared test not significant). Figure 2 shows the changes of FEV<sub>1</sub>-yr<sup>-1</sup> as percentage of the mean FEV<sub>1</sub>, i.e. the %ΔFEV<sub>1</sub> (100 x ΔFEV<sub>1</sub>/mean FEV<sub>1</sub>).

Figure 3 shows the regression lines and equations of the ΔFEV<sub>1</sub>, “normalized” (ΔFEV<sub>1</sub>-ht<sup>-3</sup>) expressed as ml·yr<sup>-1</sup>·m<sup>-3</sup> [27].

Analysis of the relationship between changes in FEV<sub>1</sub>, and the initial values of CC, slope of phase III, MMEF, Vmax<sub>25</sub> showed a significant negative relationship between the decline of FEV<sub>1</sub> and CC only in group III (r=0.05) and in group IV (p<0.05). Vmax<sub>25</sub> was significantly related (p<0.05) to ΔFEV<sub>1</sub> only in group IV. The values of MMEF and slope of phase III showed no significant relationships with FEV<sub>1</sub> decline in any of the four groups.

Discussion

Many papers have described the excessive decline of FEV<sub>1</sub> in smokers, regardless of presumed early small airways dysfunction [27, 28]. It is known that tests of small airways function can identify the smokers, however, this finding does not prove that the tests detect pathological changes that will progress to disabling chronic disease [29, 30].

Since our aim was to discover whether functionally defined SAO represents the starting point of chronic airflow limitation, only subjects with normal FEV<sub>1</sub> and FVC (both >80% pred) participated in the study. We think that the only way to determine the predictive value of the test of “small airways” is to compare the rate of decline in FEV<sub>1</sub> in various subgroups: smokers and nonsmokers, with and without presumed small airways dysfunction. In a longitudinal study of pulmonary function, over a period of 6 yrs, we investigated the relationship between decline of FEV<sub>1</sub> over time and four other measures of pulmonary function at initial survey (MMEF, CC, slope of phase III, Vmax<sub>25</sub>).

Our data show a highly significant relationship of ΔFEV<sub>1</sub> with age in the four groups studied. The observed changes in FEV<sub>1</sub> in our group are within the range reported by other longitudinal studies [31].

The regression lines show that the apparent age of onset of decline in FEV<sub>1</sub> was close to 23 yrs, without significant differences among the groups. Although other studies have suggested that a systematic decline in FEV<sub>1</sub> may not begin before 35 yrs of age, the presence of “learning effect” could explain the earlier age of decline that we have found [25].

The comparison of the slopes of the four regression lines (fig. 1) suggests that the mean values of the slopes do not differ from one group to another.

The analysis of covariance, for evaluating whether FEV<sub>1</sub> decline is more rapid in subjects with SAO compared to controls, suggests that there are also no differences in mean FEV<sub>1</sub> decline at an extrapolated higher age (e.g. 55 yrs).
We have evaluated the % ΔFEV₁, according to Burrows et al. [25] (fig. 2) because the same degree of FEV₁ decline in absolute value could have a different clinical significance: of little importance in subjects with a large initial FEV₁; more important in subjects with a lower initial FEV₁. Also, in this case the regression in groups and the analysis of covariance suggested that FEV₁ decline was not significantly different among the four groups.

FEV₁ is also related to body size. For a better population comparison the rates of FEV₁ decline were "normalized" dividing ΔFEV₁ by the cubed height of the subject [27] (figure 3). However, the statistical analysis suggests that this parameter also was not different among the groups.

In order to assess SAO we evaluated three measures of pulmonary function: MMEF, Vmax₂₅, and CC.

The question of whether MMEF is really a test of SAO has been debated for many years [24]. Low values for MMEF in combination with normal values of the other parameters (FVC, FEV₁, etc) are often indicative of early small airways abnormality [32, 33]. McFadden et al. [34] showed that in a group of 53 smokers with normal values of ratio FEV₁/VC, more than 80% had an abnormal MMEF (<60% pred).

Vmax₂₅ and CC are considered valid tests of small airways function, presumably because the lower end of the flow-volume curve and the analysis of the single-breath nitrogen test are more sensitive to abnormalities in peripheral airways and reflect the mechanical properties of poorly ventilated areas of the lung [9, 35, 36].

In agreement with others [5, 7] we found that only initial values of CC were related to the changes in FEV₁ over 6 yrs, but the relationship was restricted to the subjects of group IV (SAO, current smokers) (p<0.01). The relationship was weaker in group III (SAO, non-smokers), (p<0.05). The slope of phase III did not correlate with FEV₁ decline unlike the data of Olofsson et al. [8]. One explanation may be the age of the study population [5], our subjects were younger than those of Olofsson et al.

The linear regression of FEV₁ decline on age, of "percentage" and "height-normalized" FEV₁ were not significantly different among subjects with and without abnormal CC.

In conclusion, our findings suggest that, in young adults with normal values of FEV₁ and not exposed to occupational pollution [2-4], the presence of functional characteristics of SAO has no prognostic value for the development of chronic airflow limitation, at least as indicated by FEV₁ decline.

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References


RÉGRESSION DU VEMS CHEZ DES ADULTES JEUNES ASYMPTOMATIQUES: RELATIONS AVEC QUELQUES TESTS DE LA FONCTION DES PETITÉS VOIES AÉRIENNES. L. MARAZZINI, G. CARIGIOLI, B. MASTROPAUSCA, A. PELUCHI.
RÉSUMÉ: Le but de cette étude est d'établir si certains tests proposés comme diagnostiques de l'obstruction des petites voies aériennes (SAO) sont utiles pour identifier les sujets qui ont un risque de développer une limitation chronique des courants aériens. 85 travailleurs bien portants de sexe masculin (46 non-fumeurs et 39 fumeurs, âge moyen 21 à 41 ans), vivant dans la même région et sans exposition à des polluants professionnels, ont été examinés à deux reprises à un intervalle de 6 ans. Lors de la première enquête, 39 avaient des signes fonctionnels d'atteinte des petites voies aériennes sous forme d'une des anomalies suivantes: débit expiratoire moyen maximum <65% des valeurs prédites (py), débit maximum à 25% <60% de py; 46 d'entre eux avaient des valeurs fonctionnelles dans les limites de la norme. Nous avons considéré quatre sous-groupes: les fumeurs et les non-fumeurs, avec ou sans obstruction des petites voies aériennes. Le taux de diminution du VEMS, la diminution du VEMS en % (ΔVEMS) et le rapport ΔVEMS/CC ont été évalués et comparés dans les sous-groupes. Les valeurs initiales de certains tests spécifiques (MMEF, Vmax, CC et pente de la phase III) ont été examinées pour la présence de relations possibles avec le déclin du VEMS. L'analyse statistique de nos données montre que seul CC est en relation avec la diminution du VEMS. Toutefois, il n'y avait pas de différence significative du déclin du VEMS entre les sous-groupes. Nous concluons que chez les adultes jeunes, les anomalies fonctionnelles caractéristiques de l'obstruction des petites voies aériennes ne permettent pas de prédire le développement ultérieur d'une obstruction chronique des voies aériennes. Eur Respir J., 1989, 2, 817-821