# Relationship between Chronic Dyspnea and Expiratory Flow Limitation in Patients with Chronic Obstructive Pulmonary Disease

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**The purpose of this study was to assess whether expiratory flow limitation (FL), as measured by applying negative pressure at the mouth during tidal expiration, is a better predictor of dyspnea than routine spirometry measurements. The study population consisted of 117 ambulatory patients with COPD. Dyspnea was assessed according to the ATS-DLD respiratory Questionnaire. Expiratory flow limitation was measured in supine and sitting positions, and expressed as a percentage of the expired control tidal volume affected by flow limitation (FL, % VT). Using Spearman's rank correlation ($r_s$), we found that the correlation of dyspnea scale with FL was stronger ($r_s > 0.5$) than with FVC ($r_s < -0.3$) or $FEV_1$ ($r_s < -0.4$) in both positions. In a multiple regression analysis FL remained the best predictor of dyspnea scale even after adjustment for $FEV_1$ (% pred). Finally, FL was almost as sensitive as $FEV_1$ (% pred) but much more specific in assessing the severity of dyspnea scale. These findings suggest that expiratory flow limitation as measured by the negative expiratory pressure technique may be more useful in the evaluation of dyspnea in patients with COPD than spirometry measurements. Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease.**

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Dyspnea, especially on physical exertion, is the predominant complaint of patients with chronic obstructive pulmonary disease (COPD), and it is often the reason for seeking medical attention. The sensation of difficult or uncomfortable breathing is probably the single most important factor that limits the ability of patients with severe COPD to function on a day-to-day basis. Despite its frequency, the mechanisms contributing to dyspnea are not well understood and are likely to be multifactorial (1, 2). Recently, there has been increasing interest in the use of subjective measures of dyspnea in the assessment of exercise tolerance and treatment efficacy in patients with COPD (3), as well as in their clinical management (4, 5).

Intuitively, one would expect patients with the most severe airway obstruction, as assessed with routine lung function measurements, to be the most dyspneic. However, some patients with severe airway obstruction are minimally symptomatic, whereas others with little objective dysfunction appear to be very dyspneic (6). Several studies have investigated the correlation between dyspnea and routine lung function. An early study by Burrows and coworkers (7) has shown a statistically significant correlation between the level of chronic dyspnea and the degree of airway obstruction as expressed by $FEV_1$; however, this correlation was weak. Subsequent studies employing newer scaling techniques to quantify breathlessness found either no statistically significant correlation with routine lung function measurements (3, 6) or weak correlations (7-9). These findings are not surprising given the common clinical observation that the severity of dyspnea varies considerably among patients with similar values of $FEV_1$ (6).

Recent studies (10, 11) have provided evidence that the intensity of dyspnea during exercise in patients with COPD is closely linked to dynamic pulmonary hyperinflation. The latter condition, which is said to occur when breathing takes place from lung volumes higher than the relaxation volume of the respiratory system (Vr), is commonly a direct consequence of expiratory flow limitation (12, 13). The fact that patients with severe COPD may be flow-limited even during resting tidal breathing has been long recognized (13). Accordingly, there may be a closer association of dyspnea with expiratory flow-limitation than with $FEV_1$ or other routine lung function indices.

Originally, direct assessment of expiratory flow limitation was based on determination of isovolume relationships between flow and transpulmonary pressure, which is time-consuming and invasive (12, 14). This has led to the proposal by Hyatt in 1961 (14) that expiratory flow limitation should be assessed by comparing tidal with maximal flow-volume ($\dot{V}$-V) curves. However, this approach may lead to erroneous conclusions (15). Recently, a simple and noninvasive approach, namely, the negative expiratory pressure (NEP) technique, has been developed to detect expiratory flow limitation (15, 16). This technique, which does not re-

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quire performance of FVC maneuvers on the part of the subject, consists in applying a negative pressure at the mouth during tidal expiration and comparing the ensuing flow-volume curve with that of the previous control expiration. It can be applied in different body positions, both at rest and during muscular exercise. The NEP technique has been validated in two case-series, one comprising 12 mechanically ventilated patients (16) and the second comprising 26 stable ambulatory patients with COPD (15).

The purpose of the present study was to evaluate the potential of expiratory flow limitation, as measured with the NEP technique, in the clinical assessment of dyspnea in patients with COPD. Specifically, our objective was to determine whether in patients with COPD flow-limitation is a better predictor of dyspnea than the routine spirometry measurements ($FEV_1$, FVC, and $FEV_1/FVC$). This information has potential usefulness in the care of such patients since dyspnea greatly influences patient's overall health status (4).

## METHODS

### Study Design and Population

A cross-sectional study was carried out on 117 consecutive ambulatory patients with COPD (75 men and 42 women). All were in a stable clinical and functional state and were recruited from the respiratory outpatient clinic of the Montreal Chest Hospital Center on the basis of a physician's diagnosis of COPD. Their anthropometric characteristics and lung function data are given in Table 1. Each patient gave informed consent, and the study protocol was approved by the Institutional Ethics Committee.

### Questionnaire

All eligible patients were invited to complete a modified version of the standardized ATS respiratory questionnaire (17), which includes questions concerning the presence of other respiratory diseases and/or significant systemic illnesses or psychiatric disorders that may contribute to breathlessness (Table 2). All questions related to respiratory symptoms and illnesses were retained whereas questions on occupational exposure, professional status, and smoking history were replaced by those from the standardized questionnaire used in the study of Lung Health and Canadian Environment (18). Additional questions concerning the level of education, presence of systemic illnesses or psychiatric disorders that may contribute to breathlessness, and symptoms caused by sleep apnea such as snoring, excessive daytime sleepiness, and sleep maintenance insomnia were added at the end of the questionnaire, as suggested by the ATS (17). The questionnaire was self-administered. The respiratory symptoms analyzed included chronic cough (defined as cough for 3 mo or more of the year), and chronic phlegm (defined as sputum production for 3 mo or more of the year). In accordance to ATS guidelines (17), smoking status was classified as follows: NS for nonsmoker (never met criteria of being a regular smoker at any time), FS for former smoker (regular smoker up to at least 2 mo before the study), and CS for current smoker (regular smoker up to 1 mo before the study). According to the standardized Lung Health and Canadian Environment questionnaire (18), educational level was stratified as follows: primary level (including none and primary level), secondary level, and college level (including college and university level). The severity of chronic dyspnea was assessed by the ATS questionnaire and rated according to the dyspnea scale proposed by the Medical Research Council (MRC) (19) with minor modifications (Table 3).

### Measurements

*Spirometry and thoracic gas volume measurements.* Spirometry was performed on the same day as the dyspnea was graded. FVC and $FEV_1$ were measured both seated and supine using the Spiro Analyzer ST-250R Spirometer (Fukada Sangyo Co., LTD, Tokyo, Japan). This system, which meets the ATS standards (20), was calibrated every day with standardized techniques according to the guidelines of the American Thoracic Society (20). In 83 patients, thoracic gas volumes were also obtained in seated position with a pressure/flow whole body plethysmograph (Autobox 2800; Sensor-medics Inc., Yorba Linda, CA). The predicted values for routine spirometry and thoracic gas volumes were those of Morris and

TABLE 1

ANTHROPOMETRIC AND LUNG FUNCTION DATA OF 117 PATIENTS WITH COPD*

| | Men ($n$ = 75) | Women ($n$ = 42) |
|---|---|---|
| Age | 70 ± 8 | 69 ± 9 |
| Height, cm | 167 ± 7 | 157 ± 6† |
| Weight, kg | 72 ± 18 | 64 ± 12† |
| $FEV_1$, % pred | 34 ± 14 | 40 ± 15† |
| FVC, % pred | 63 ± 17 | 62 ± 18 |
| $FEV_1/FVC$, % pred | 54 ± 16 | 63 ± 20† |
| MRC dyspnea scale | 2.6 ± 1.4 | 2.8 ± 1.4 |

* Values are mean ± SD.
† $p < 0.05$ comparing men and women.

TABLE 2

PATIENTS CHARACTERISTICS

| | Men ($n$ = 75) | | Women ($n$ = 42) | |
|---|---|---|---|---|
| | ($n$) | (%) | ($n$) | (%) |
| Chief complaint | | | | |
| None | 5 | 7 | 1 | 2 |
| Dyspnea | 27 | 36 | 26 | 62 |
| Cough and phelgm | 11 | 15 | 4 | 10 |
| Cigarette smoking history | | | | |
| Nonsmoker | 4 | 5 | 5 | 12 |
| Former smoker | 49 | 65 | 24 | 57 |
| Current smoker | 21 | 28 | 14 | 34 |
| Treatment | | | | |
| Oral corticotherapy | 14 | 19 | 6 | 14 |
| Continuous $O_2$ therapy | 2 | 3 | 3 | 7 |
| History | | | | |
| Allergy | 6 | 8 | 11 | 26 |
| Occupational exposure history | 39 | 52 | 6 | 14 |
| Other associated respiratory diseases | | | | |
| History of asthma | 7 | 9 | 6 | 14 |
| Obstructive sleep apnea | 2 | 3 | 1 | 2 |
| Lung cancer | 3 | 4 | 0 | 0 |
| Associated systemic diseases | | | | |
| None | 33 | 44 | 19 | 45 |
| Coronary artery disease | 21 | 28 | 13 | 31 |
| Systemic arterial hypertension | 14 | 19 | 12 | 29 |
| Highest educational level | | | | |
| Up to primary | 39 | 52 | 15 | 36 |
| Secondary | 20 | 27 | 16 | 38 |
| College and university | 15 | 21 | 11 | 26 |

TABLE 3

MODIFIED MRC DYSPNEA SCALE*

| Category | Degree | |
|---|---|---|
| 0 | None | Not troubled by dyspnea |
| 1 | Slight | Troubled by shortness of breath when hurrying on the level or walking up a slight hill |
| 2 | Moderate | Walks slower than people of the same age on the level because of breathlessness |
| 3 | Moderately severe | Has to stop because of breathlessness when walking at own pace on the level |
| 4 | Severe | Stops for breath after walking about 100 yards or after a few minutes on the level |
| 5 | Very severe | Too breathless to leave the house or breathless when dressing or undressing |

* Based on the information obtained using the ATS-DLD respiratory Questionnaire (17) to classify dyspnea according to the categories proposed by the MRC (cf 8, 9).

TABLE 4

CLASSIFICATION OF VENTILATORY IMPAIRMENT INTO FIVE CATEGORIES ACCORDING TO $FEV_1$*

| $FEV_1$ (% *pred*) | Category | Degree |
|---|---|---|
| 70–100 | 0 | Mild |
| 60–69 | 1 | Moderate |
| 50–59 | 2 | Moderately severe |
| 35–49 | 3 | Severe |
| < 35 | 4 | Very severe |

* From Burrows and Lebowitz (22). The $FEV_1$/FVC ratio must be below the normal range.

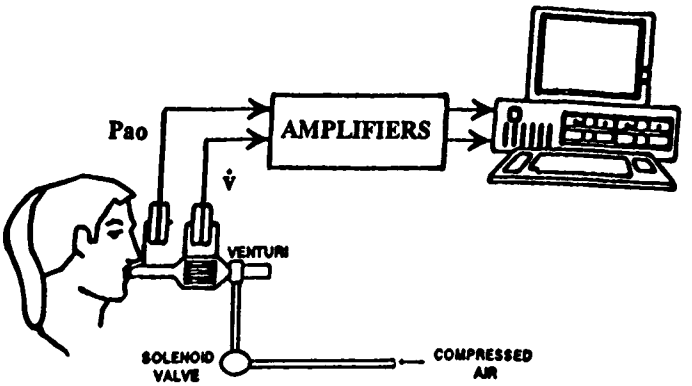


*Figure 1.* Schematic diagram of equipment setup. Pao = pressure at airway opening; V̇ = flow.

coworkers (21). In 27 patients, $Pa_{O_2}$ and $Pa_{CO_2}$ were measured with a blood gas analyzer (ABL 330; Radiometer, Copenhagen, Denmark). Ventilatory impairment was classified on the basis of $FEV_1$ (% pred) into the five categories proposed by Burrows and Lebowitz (22) (Table 4).

*Negative expiratory pressure.* The experimental setup is depicted in Figure 1. A flanged plastic mouthpiece was connected in series with a Fleisch no. 2 pneumotachograph (Fleisch, Lausanne, Switzerland) and a Venturi device capable of generating a negative pressure during expiration (Aeromech Devices Ltd., Almonte, Ontario, Canada). One end of the device was open to atmosphere, whereas the other was connected to a cone of the pneumotachograph. Standard tubing (ID = 8 mm) was used to connect a side port on the Venturi device, via an electrically operated solenoid valve, to a cylinder of compressed air. The length of the tubing between the cylinder and the valve was 4 m, and that between the valve and the Venturi device was 1 m. A pressure regulator on the compressed air cylinder was used to obtain a preset level of NEP at the airway opening (−5 cm $H_2O$). The solenoid valve (Ascott electrical valve model no. 8262G2; Ascoletric Ltd., Ontario, Canada), which was controlled by a computer (Direc Physiologic Recording System; Raytech Instruments, Vancouver, British Columbia, Canada), has an opening time of 28 ms. The solenoid valve was activated when the expiratory flow reached a preset threshold value (30 ml/s in the present study), and it could be kept open for any desired time. With this threshold, the overall time required to trigger the valve and reach the preset level of NEP ($T_{NEP}$) was about 100 ms from the onset of expiration. However, $T_{NEP}$ could be prolonged to any desired time by introducing a computer-controlled delay time between the time when the flow reached the preset threshold and the triggering of the valve. Airflow (V̇) was measured with the heated pneumotachograph connected to a differential pressure transducer (Validyne MP45, ± 2 cm $H_2O$; Validyne Corp., Northridge, CA). The pneumotachograph was linear over the experimental range of flow. Artifacts on the flow record caused by common-mode rejection ratio (CMRR) were negligible (23). Volume was obtained by numerical integration of the flow signal. Pressure at the airway opening (Pao) was measured through a side port on the mouthpiece using a differential pressure transducer (Validyne MP45, ± 100 cm $H_2O$). The pressure transducer was calibrated before and after each study with a water manometer. The breathing assembly had a dead space of 50 ml, and its pressure-flow relationship was characterized by the following equation: $P = 0.45\ \dot{V} + 0.02\ \dot{V}^2$ ($R^2 = 0.996$), where pressure is in cm $H_2O$ and flow is in L/s. The pressure, volume, and flow signals were amplified (ADC Bridge amplifier −ACB module; Raytech Instruments), low-pass filtered at 50 Hz and digitized at 100 Hz by a 16 bit analog-to-digital converter (Direct Physiologic Recording System, Raytech Instruments). The digitized data were stored on the computer hard disk for subsequent analysis. Data analysis was performed using ANADAT software (version 5.1; RMT-InforDat Inc., Montreal, Quebec, Canada). During the study, the time course of flow, volume, and pressure were continuously monitored on the screen of the computer, together with the corresponding flow-volume curves.

*Potential hazards to patients.* In line with a previous study (15), application of NEP was not associated with unpleasant sensations or cough. Application of negative airway pressure may result in increased airway resistance because of extrathoracic airway narrowing with a concomitant decrease of expiratory flow (24). In our patients, however, with NEP expiratory flow either increased (reflecting absence of flow limitation) or did not change, except transiently (reflecting presence of flow limitation). There was no instance in which NEP resulted in a substantial decrease of expiratory flow below the corresponding control values. This implies that, if anything, the changes in airway resistance caused by our low level of NEP (−5 cm $H_2O$) were probably relatively small. In this connection it should be noted that Valta and coworkers (16) have used added resistances to detect flow limitation, and they found that in flow-limited patients the expiratory flow did not change unless a very high expiratory resistance was added.

### Procedure

Each patient completed the study questionnaire on the same day that spirometry and NEP measurements were carried out. All subjects were studied both seated upright in a comfortable chair and lying supine on a comfortable couch, in random order. They were asked to breathe room air through the equipment assembly (Figure 1) with the noseclip on. In order to become accustomed to the apparatus and procedure each patient had an initial 10- to 15-min trial run with the NEP equipment. The pattern of breathing was continuously monitored on the computer screen. After reaching steady-state breathing, a series of test breaths were performed in which NEP of −5 cm $H_2O$ was applied at the beginning of expiration and maintained throughout the ensuing expiration. The opening of the valve was accomplished without the subject's anticipation. The $T_{NEP}$ was adjusted such that it coincided with peak expiratory flow, and NEP was applied for a duration corresponding to control expiratory time. The test breath was the breath during which the NEP was applied during expiration, and the preceding expiration served as control. A series of three to five test breaths separated by periods of quiet breathing were made both seated and supine. The FVC maneuvers were performed in a standardized fashion: rapid inspiration from FRC without an end-inspiratory pause (25).

### Detection and Assessment of Degree of Flow-Limitation

Flow limitation is a term often used to indicate that there is a reduction in the maximal flows that can be achieved during the forced expiratory maneuver. In the present study the term was used to indicate that expiratory flow rates achieved during tidal breathing are the maximal achievable under the prevailing conditions, including posture.

The expiratory flow-volume (V̇-V) loops generated with NEP in seated and supine position were compared by superimposition with those obtained during the immediately preceding breaths (Figure 2). The volume signal was corrected for any offset based on the assumption that inspired and expired volumes of the preceding breath were identical (26). The portion of the tidal expiration over which there was no appreciable change in flow with NEP (i.e., the portion of the tidal expiration over which the expiratory flows were identical during the control and test expirations) was considered as flow-limited and was expressed as a percentage of the expired control tidal volume (% $V_T$) (16). During the early part of tidal expiration, which is characterized by increasing flow (Figure 2), there cannot be expiratory flow limitation (15). Accordingly, in spontaneously breathing patients, flow limitation is necessarily always less than 100% $V_T$ (15). In the absence of preexisting flow-limitation,

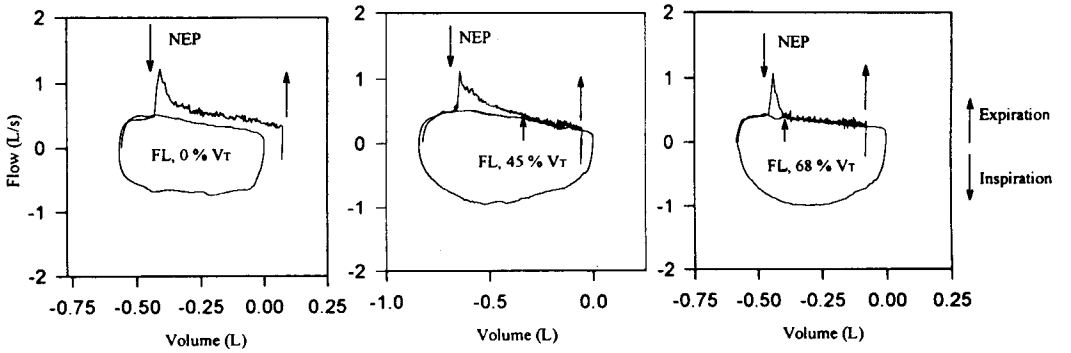


***Figure 2.*** Flow-volume loops of test breaths and preceding control breaths of three representative patients with different degrees of expiratory flow-limitation: No flow-limitation (FL) (*left panel*), FL over less than 50% of control expired tidal volume (VT) (*middle panel*), FL over more than 50% VT (*right panel*). Long arrows indicate points at which NEP was applied and removed. Short arrows indicate onset of flow limitation. Zero volume is end-expiratory lung volume of control breaths.

the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow, whereas in flow-limited subjects NEP should enhance dynamic airway compression downstream from the flow-limiting segments, without substantial effect on pressure or flow upstream. Accordingly, in flow-limited subjects, expiratory flow does not change with NEP, except for a brief flow transient (spike), which is thought to mainly reflect sudden reduction in volume of the compliant oral and neck structures (15, 16). To a lesser extent, however, enhanced dynamic airway compression and a small artifact caused by the common-mode rejection ratio of the system for measuring flow also contributed to such flow transients. In line with previous studies (15, 16), after the application of NEP the expiratory flow either increased (reflecting absence of flow limitation) or did not change (reflecting presence of flow limitation). There was no instance in which application of NEP resulted in a sustained decrease of expiratory flow below the corresponding control values.

The degree of flow limitation was assessed using three different flow limitation (FL) indices:

1. As a continuous variable in the form of FL % VT in both seated and supine position (*see above* and Figure 2). In this case, absence of flow limitation is labeled 0% VT.
2. As a discrete variable in the form of a three-categories classification (three-point FL score): (*1*) not flow-limited both supine and seated; (*2*) flow-limited supine but not seated; and (*3*) flow-limited both supine and seated. This classification has been previously used by Koulouris and coworkers (15) in stable ambulatory patients with COPD. They found, similar to the present findings, that all patients with COPD who were flow-limited seated were also flow-limited supine, whereas many patients who were flow-limited supine were not flow-limited seated.
3. Again as a discrete variable in the form of a five-categories classification (five-point FL score) that combines the above two indices (Table 5). The 5-point FL score is based on the observation that during the resting breathing expiratory flow limitation is an earlier manifestation of COPD in the supine than in the sitting position (15). As a result, patients who at rest are flow-limited only in the supine position would be expected to exhibit flow limitation with concomitant dynamic hyperinflation and dyspnea at higher exercise levels than patients who at rest are flow-limited also in the sitting position. Indeed, patients with FL > 50% VT in the sitting position should exhibit enhanced dynamic hyperinflation and dyspnea at low levels of muscular effort such as those required to leave the house or when dressing or undressing (Table 3).

The reproducibility of the MRC dyspnea scale and the FL measurements was assessed in a pilot study on 10 subjects. These subjects were chosen from the outpatient clinics of the Saint-Luc Hospital. Five of them were selected based on two criteria: a physician's diagnosis of COPD and stable clinical dyspnea rating (MRC scale) of 3 to 5. The five others,

**TABLE 5**

**CLASSIFICATION OF FLOW-LIMITATION (FL) INTO FIVE CATEGORIES ACCORDING TO PERCENT CONTROL TIDAL VOLUME ENCOMPASSED BY FL (FL, % VT) AND BODY POSITION**

| Supine | Seated | Category | Degree |
|---|---|---|---|
| No FL | No FL | 0 | None |
| FL < 50% VT | No FL | 1 | Mild |
| FL > 50% VT | No FL | 2 | Moderate |
| FL | FL < 50% VT | 3 | Severe |
| FL | FL > 50% VT | 4 | Very severe |

*Definition of abbreviations*: 0 = not flow-limited either seated or supine; 1 = flow-limited < 50% VT supine but not flow-limited seated; 2 = flow-limited > 50% VT supine but not flow-limited seated; 3 =flow-limited < 50% VT seated and flow-limited supine; 4 = flow-limited > 50% VT seated and flow limited supine.

chosen from the list of nonrespiratory outpatient clinics did not have any respiratory disease and did not complain of dyspnea. They were scheduled for two visits, 2 wk apart. At both visits, the 10 patients performed the same tests. They completed the modified version of the ATS-DLD questionnaire and performed the spirometry and the NEP tests on the same day. The reproducibility of both, the MRC dyspnea scale and the FL measurements, in this sample was 95%. The same degree of flow limitation, as calculated from the comparison of the expiratory flow-volume curve during which the NEP was applied and that of the previous control expiration and categorized according to the five-point FL score (explained in the methods and in Table 2), was observed with nine of the ten subjects in both positions, sitting and supine, and at both visits. However, one patient with COPD who was flow-limited over less than 50% of his VT in the supine position during his first visit, became flow-limited over more than 50% of his VT in the same position during his second visit. Similarly, the same dyspnea scale was reported by nine of the 10 subjects. One patient with COPD reported higher scale on the second visit (MRC dyspnea scale: 2 to 3).

### Data Analysis

The relationship between dyspnea scale, so measured, and the independent variables, namely, the routine spirometry measurements ($FEV_1$, FVC, and $FEV_1$/FVC) and the flow-limitation indices, were first examined using Spearman's rank correlations ($r_S$) (27). A nonparametric test was chosen in order to minimize assumptions about distribution of data.

Next, multiple regression analysis was performed to evaluate $FEV_1$ and FL as independent or complementary predictors of dyspnea scale (dependent variable) while controlling for the effects of other possible determinants of dyspnea such as age, sex, height, weight, smoking status, and educational level. Because the outcome variable, dyspnea scale, was a discrete categorical variable (Table 3), the general multiple regres-

TABLE 6

ANTHROPOMETRIC AND LUNG FUNCTION DATA OF 117 PATIENTS WITH COPD STRATIFIED ACCORDING TO THE THREE-CATEGORY FL SCORE*

| | No FL | FL Supine | FL Supine and Seated |
|---|---|---|---|
| Number of subjects | 26 | 22 | 69 |
| Sex, M/F | 15/11 | 13/9 | 47/22 |
| Age, yr | 72 ± 8 | 69 ± 8 | 69 ± 10 |
| Height, cm | 163 ± 11 | 163 ± 6 | 164 ± 8 |
| Weight, kg | 68 ± 18 | 66 ± 11 | 70 ± 17 |
| $FEV_1$, % pred† | 46 ± 17‡ | 39 ± 17‡ | 31 ± 11 |
| FVC, % pred† | 69 ± 18‡ | 61 ± 16 | 60 ± 16 |
| $FEV_1/FVC$, % pred† | 65 ± 20‡ | 64 ± 13‡ | 52 ± 17 |
| MRC dyspnea sale† | 1.3 ± 1.2‡ | 2.0 ± 0.8‡ | 3.4 ± 1.2 |
| Number of subjects | 17 | 13 | 53 |
| TLC, % pred† | 119 ± 19‡ | 121 ± 13‡ | 134 ± 20 |
| FRC, % pred† | 134 ± 24‡ | 143 ± 19 | 163 ± 40 |
| RV, % pred† | 154 ± 33‡ | 163 ± 22‡ | 197 ± 46 |
| RV/TLC, % pred† | 130 ± 23‡ | 135 ± 18 | 146 ± 21 |
| Number of subjects | 6 | 5 | 16 |
| $Pa_{O_2}$, mm Hg | 75 ± 12 | 72 ± 18 | 68 ± 11 |
| $Pa_{CO_2}$, mm Hg† | 42 ± 4‡ | 37 ± 3‡ | 48 ± 6 |

* Values are means ± SD.
† ANOVA: analysis of variance for three groups, $p < 0.05$.
‡ ANOVA: first and/or second groups significantly different from third group, $p < 0.05$.

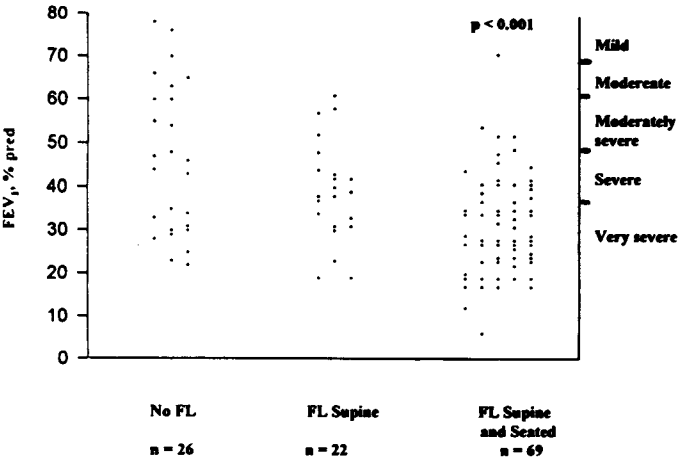


*Figure 3.* Individual values of $FEV_1$ (% pred) and flow limitation, stratified according to the three-point flow limitation (FL) score, of 26 patients with COPD who were not flow-limited either seated or supine, 22 who were flow-limited only supine, and 69 who were flow-limited both seated and supine; p value refers to significant difference between No FL and FL supine and seated. Also shown on the right ordinate is the categorical classification of the degree of ventilatory disability according to Table 4.

sion model was chosen instead of the multiple linear regression model. The independent variables comprised $FEV_1$ (% pred), age, height, and weight, which were expressed as continuous variables, whereas sex, smoking history, educational level, and 5-point FL score were taken as discrete variables. The strongest contributors to dyspnea were selected by stepwise multiple regression analysis.

Finally, in order to evaluate which independent variable, FL or $FEV_1$, is a better tool for assessing the intensity of dyspnea scale, a two-by-two table was constructed using dyspnea scale as a gold standard. For this sensitivity analysis, dyspnea scale was rated according to Table 3, whereas rating for $FEV_1$ was made according to Table 4, and for the degree of flow limitation according to the 5-point FL score in Table 5. Sensitivity analysis was performed with two cutoff points: (*1*) dyspnea versus no dyspnea *and* flow limitation versus no flow limitation *compared with* dyspnea versus no dyspnea *and* mild versus moderate-to-severe airway obstruction; (*2*) Severe dyspnea versus nonsevere dyspnea *and* severe flow limitation versus nonsevere flow limitation *compared with* severe dyspnea versus nonsevere dyspnea *and* severe versus nonsevere airway obstruction.

Statistical analysis was carried out using one-way analysis of variance (ANOVA) and the Student-Neumen-Keuls test for multiple comparisons. The conventional level of statistical analysis ($p < 0.05$) was used for all analyses.

## RESULTS

As shown in Table 6, most of the 117 patients with COPD studied exhibited expiratory flow limitation during resting breathing in either supine position alone (19%) or both seated and supine (59%). Although the anthropometric variables did not differ significantly among the three groups, the lung function data and the degree of dyspnea scale did. The individual values of $FEV_1$ (% pred) stratified according to the three-point FL score are depicted in Figure 3. Though, on average, the patients who were flow-limited both seated and supine had significantly lower $FEV_1$ (Table 6), there was considerable scatter of the data. Indeed, 60% of the non-flow-limited group had a $FEV_1$ below 49% pred and would be classified as having severe-to-very severe airway obstruction. Similar results were also found in terms of FVC and $FEV_1/FVC$ (% pred).

The individual values of the severity of dyspnea (MRC scale) stratified according to the three-point FL score are shown in Figure 4. Though the scatter was still substantial, only three patients (11%) without flow limitation had moderately severe-to-severe dyspnea scale, and none had very severe dyspnea scale. In contrast, eight patients (31%) without flow limitation had very severe ventilatory impairment ($FEV_1 < 35\%$ pred) (Figure 3). The Spearman's rank correlation coefficient of the three-point FL score with dyspnea scale was 0.5 ($p < 0.001$), whereas that with $FEV_1$ (% pred) was less than 0.38 (Table 7).

The presence of flow-limitation at rest implies concomitant dynamic pulmonary hyperinflation (12, 13, 28). Predictably, the patients with COPD who were flow-limited both seated and su-

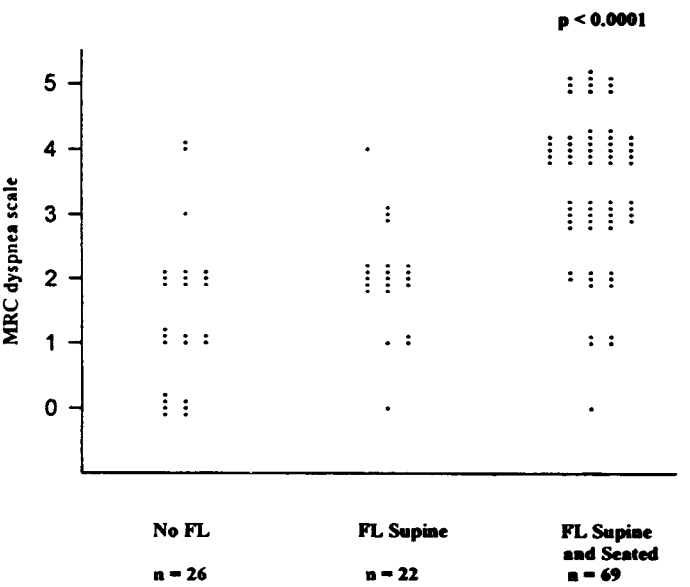


*Figure 4.* Individual values of degree of dyspnea (MRC dyspnea scale) and flow limitation (three-point FL score) as in Figure 3; p value refers to significant difference between No FL and FL supine and seated.

TABLE 7

SPEARMAN'S RANK CORRELATION COEFFICIENTS OF MRC DYSPNEA SCALE WITH VARIOUS LUNG FUNCTION TESTS AND DEGREE OF FLOW-LIMITATION (FL, % VT)*

| | Seated | Supine |
|---|---|---|
| FL, % VT | 0.54§ | 0.66§ |
| $FEV_1$, % pred | −0.37§ | −0.33§ |
| FVC, % pred | −0.22† | −0.21† |
| $FEV_1$/FVC, % pred | −0.30‡ | −0.23‡ |

* Flow limitation (FL, % VT) and lung function data are expressed as continuous variables.
† $p < 0.05$.
‡ $p < 0.01$.
§ $p < 0.001$.

pine exhibited significantly higher FRC than did those who were not flow-limited either seated or supine (Table 6). We also found that in the patients who were flow-limited both sitting and supine the $Pa_{CO_2}$ was significantly higher compared with that in the other two groups of patients.

The Spearman's correlation coefficients of dyspnea scale with various lung function tests and the degree of flow limitation (FL, % VT) are shown in Table 7 for both seated and supine positions. In this instance the degree of flow limitation is assessed as a continuous variable, i.e., as percentage fraction of the control expired tidal volume that is flow-limited (% VT) (Figure 2). Although dyspnea scale was significantly correlated with $FEV_1$, FVC, and $FEV_1$/FVC (% pred) in both positions, the correlation coefficients were much higher with the degree of flow limitation, particularly in supine position. Because the five-point FL score combines the effects of posture (three-point FL score) and extent of tidal expiration encompassed by flow limitation (FL, % VT), it is not surprising that its correlation with dyspnea scale was high, the Spearman's rank correlation coefficient amounting to 0.73.

### Multiple Regression Analysis

In the general multiple regression model with MRC dyspnea scale as the outcome, the $FEV_1$ (%pred), age, sex, height, weight, smoking history, and educational level as the explanatory covariables, $FEV_1$ (% pred), smoking history, and height were the only significant predictors of dyspnea scale (Model 1 in Table 8). In this model, $FEV_1$ (% pred) was the strongest predictor of dyspnea scale, accounting for 68% of the overall variance, which amounted to 25% ($R^2 = 0.25$). However, by including the five-point FL score to the model, $FEV_1$ (% pred) as well as smoking history were no longer significant (Model 2 in Table 8). Though height remained a significant predictor of dyspnea scale, the five-point FL score became the strongest predictor of dyspnea scale, alone accounting for 90% of the overall variance ($R^2 = 0.58$). In a third model, which excluded height, sex was found to be a significant predictor of dyspnea scale (Model 3 in Table 8).

### Sensitivity Analysis

In order to evaluate which test is a better tool for assessing accurately the severity of dyspnea scale, we performed the sensitivity analysis for both $FEV_1$ and five-point FL score (Table 9). At both cutoff points (*see* METHODS), the five-point FL score and $FEV_1$ (% pred) had a sensitivity higher than 80% (as much as 96% for $FEV_1$); in contrast, the specificity of FL was much higher than that of $FEV_1$ (% pred) (80 to 87% versus 20 to 26%).

## DISCUSSION

Dyspnea is a common and often incapacitating symptom in patients with COPD. Effective management of this distressing symptom awaits a clearer understanding of the pathophysiologic mechanisms instrumental in its genesis. Although many factors have been shown to contribute to the sensation of dyspnea in COPD (1, 2), it seems reasonable to assume that mechanical factors play an important if not a predominant role (10, 11). In this study we have examined the association of chronic dyspnea with

TABLE 8

REGRESSION EQUATIONS OF MRC DYSPNEA SCALE WITH VARIOUS COVARIABLES

| | | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|
| Covariables | | Regression Coefficients | SE | Regression Coefficients | SE | Regression Coefficients | SE |
| 5-point FL SCORE | 0 | Not included | | −1.31* | 0.21 | −1.32* | 0.22 |
| | 1 | | | −0.78 | 0.23 | −0.79 | 0.23 |
| | 2 | | | −0.12 | 0.24 | −0.08 | 0.24 |
| | 3 | | | 0.69 | 0.22 | 0.73 | 0.22 |
| | 4 | | | | | Reference category | |
| Height, cm | | −0.04* | 0.01 | −0.03† | 0.01 | Not included | |
| $FEV_1$, % pred | | −0.04* | 0.01 | Not significant | | Not significant | |
| Smoking history | NS | −0.79† | 0.43 | Not significant | | Not significant | |
| | FS | −0.34 | 0.15 | | | | |
| | CS | Reference category | | | | | |
| Sex | M | Not significant | | Not significant | | −0.20† | 0.16 |
| | F | Reference category | | | | | |
| Educational level | P | Not significant | | Not significant | | Not significant | |
| | S | | | | | | |
| | C | Reference category | | | | | |
| Age, yr | | Not significant | | Not significant | | Not significant | |
| Weight, kg | | Not significant | | Not significant | | Not significant | |
| Constant | | 10.04 | | 7.37 | | 3.17 | |
| Overall variance ($R^2$) | | 0.25 | | 0.58 | | 0.56 | |

*Definition of abbreviations*: SE = standard error; NS = nonsmoker; FS = former smoker; CS = current smoker; P = none and primary level; S = secondary level; C = college and university level.
* Overall significance of covariable: $p < 0.01$.
† Overall significance of covariable: $p < 0.05$.

TABLE 9
SENSITIVITY ANALYSIS

| MRC Dyspnea Scale | Five-Category FL Score | $FEV_1$* (% pred) |
|---|---|---|
| Level 0 versus 1 to 5 | Level 0 versus 1 to 4 | Level 0 versus 1 to 4 |
| Sensitivity | 83% | 96% |
| Specificity | 80% | 20% |
| Level 0 to 3 versus 4 to 5 | Level 0 to 2 versus 3 to 4 | Level 0 to 2 versus 3 to 4 |
| Sensitivity | 85% | 90% |
| Specificity | 87% | 26% |

* Classified according to Table 4.

routine lung function tests and various FL indices assessed by the NEP technique in a series of 117 patients with COPD. Our main findings are (*1*) that dyspnea scale correlates much better with the five-point FL score than with the routine spirometry measurements; (*2*) that in multiple regression analysis, the five-point FL score was the strongest predictor of dyspnea scale, accounting for more than 90% of the overall variance in dyspnea scale; (*3*) though the five-point FL score was almost as sensitive as $FEV_1$ (% pred) in accurately assessing the severity of dyspnea scale, it showed much higher specificity.

The weak correlation found between dyspnea scale and routine spirometry measurements ($FEV_1$, FVC, $FEV_1$/FVC) is consistent with the results of most previous studies (7–9), though McGavin and coworkers (3) found no significant correlation between the subjective assessments of dyspnea and both $FEV_1$ and FVC. In some of the previous studies (3, 8, 9) the clinical ratings used to quantify chronic dyspnea differed from the MRC dyspnea scale. However, Mahler and Wells (8) have shown that the different dyspnea ratings, namely OCD (Oxygen Cost Diagram), BDI (Baseline Dyspnea Index), and MRC scale were significantly and highly correlated. In line with Burrows and coworkers (7), we found a higher correlation between dyspnea scale and $FEV_1$ ($r_s = -0.37$) than with FVC ($r_s = -0.22$) in seated position (Table 7). In contrast, Mahler and coworkers (8, 9) found that the correlation of FVC and $FEV_1$ with dyspnea scale was similar (Spearman's rank correlation coefficients: −0.41 versus −0.42). On the basis of the poor correlation between dyspnea ratings and spirometry measurements, several investigations have suggested that the dyspnea questionnaires yield important additional information to that provided by the lung function tests (20, 29). However, both sitting and supine we found that dyspnea scale correlated better with the degree of flow limitation, assessed as FL, % $V_T$, than with $FEV_1$ (% pred) (Table 7). Furthermore, the severity of dyspnea scale was significantly higher in the patients who were flow-limited both seated and supine than in those who were flow-limited only supine ($p < 0.05$) or who were not flow-limited in either position ($p < 0.001$) (Table 6). In line with a previous study (15), we also found that all 69 patients with COPD who were flow-limited while seated were also flow-limited when supine. By contrast, 22 patients were found to be flow-limited only in the supine position, probably reflecting the fact that in this position the FRC is lower than in the sitting position, with a concomitant reduction in expiratory flow reserve (15). As a result, expiratory flow limitation at rest is an earlier manifestation in supine than in sitting position (15).

The five-point FL score includes both the effects of posture on flow limitation and the extent of tidal expiration encompassed by flow limitation (FL, % $V_T$) on dyspnea. As a result, its correlation coefficient with the degree of dyspnea scale was higher than that of all variables studied ($r_s = 0.73$). It should be noted, however, that in COPD there may be factors other than ventilatory abnormalities that can contribute to the sensation of dyspnea. These include decreased arterial $P_{O_2}$ during exercise, deconditioning, alterations in venous return, and cardiac disease, which is present in many patients with COPD (30). After excluding the patients who had heart disease (29%), according to the questionnaire, Spearman's rank correlation coefficient of dyspnea scale with the five-point FL score did not change ($r_s = 0.75$).

The close relationship between our FL indices and the MRC dyspnea scale indicates that the latter is both useful and valid. Furthermore, the MRC dyspnea scale has the advantage of being simple and self-administered, and hence suitable for field studies.

The finding that dyspnea scale tended to be most severe in patients with FL > 50% $V_T$ in seated position is not surprising because it implies that dynamic hyperinflation is already present at rest, with a concomitant increase in FRC (Table 6), increased inspiratory effort caused by intrinsic PEEP, and impaired inspiratory muscle function (12, 13, 28). This should be enhanced by any further increase in ventilation caused by muscular exercise or other causes. Thus, in such patients, a higher degree of chronic dyspnea, as assessed with the MRC dyspnea scale (Table 3), is virtually axiomatic. In this connection, it should be noted that in patients with COPD enhanced pulmonary hyperinflation during muscular exercise has been shown to be an important determinant of exertional dyspnea (10, 11). Furthermore, it has been suggested that flow-limiting dynamic airway compression during tidal breathing may per se also contribute to the sensation of dyspnea (31). These findings, which were obtained when dyspnea developed in the short-term, (i.e., acute dyspnea during exercise), are consistent with the present results pertaining to chronic dyspnea.

In a study on 96 stable patients with COPD at rest, Haluszka and coworkers (32) found a significant association between $Pa_{CO_2}$ and PEEPi. Because PEEPi is a manifestation of expiratory flow limitation (13, 15), an increased $Pa_{CO_2}$ was to be expected in our patients with COPD who were flow-limited in the sitting position. Indeed, as shown in Table 6, $Pa_{CO_2}$ was significantly higher in the patients who were flow-limited in the sitting position than in those who were not flow-limited both seated and supine. Although $Pa_{CO_2}$ was lower in the former patients, the difference was not significant.

In Model 1 of the multiple regression analysis, dyspnea scale was significantly and negatively correlated with $FEV_1$ (% pred), smoking history, and height (Table 8). According to this model, taller, nonsmoking patients with COPD and high $FEV_1$ (% pred) should have lower dyspnea scale than smaller patients with COPD who smoke and have a low $FEV_1$ (% pred). This finding is in line with previous epidemiologic studies in normal subjects at rest (33) or during exercise (34). Although, according to Model 1, $FEV_1$ (% pred) was the strongest predictor of dyspnea scale, its contribution to the overall variance in dyspnea scale was no longer significant when the 5-point FL score was included in the model (Model 2 in Table 8). Furthermore, FL was a stronger predictor of dyspnea scale than $FEV_1$ (% pred), alone accounting for 90% of the overall variance in dyspnea scale ($R^2 = 0.58$).

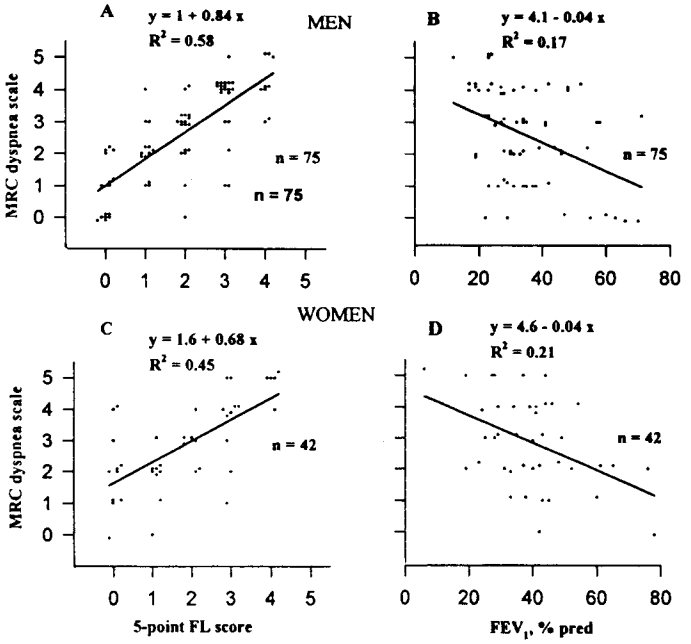


*Figure 5.* Relationship of degree of dyspnea (MRC dyspnea scale) with flow-limitation (five-point FL score) and $FEV_1$ (% pred) for men and women. Linear regression equations that were significant ($p < 0.01$), and variance ($R^2$) are also provided.

This finding is supported by recent studies (10, 11) which have shown that dynamic hyperinflation (a direct consequence of flow limitation) was the strongest predictor of dyspnea during muscular exercise. After adjustment for FL score, smoking was no longer a significant predictor of dyspnea scale (Model 2 in Table 8). In contrast, the 16% initial contribution of height to the overall variance in dyspnea scale ($R^2 = 0.25$) remained the same even after adjustment for FL score. Therefore, by adding FL score to the model, $FEV_1$ lost its role as significant predictor of dyspnea scale (33), whereas height remained an independent and significant predictor of dyspnea scale. This discrepancy may be explained by the fact that FL is superior to $FEV_1$ in predicting the intensity of dyspnea scale related to the disease (COPD) itself, whereas height, a characteristic of the subject rather than of the disease, constitutes by itself an independent determinant of dyspnea scale (33). Given the fact that women tend to be shorter than men (Table 1), the role of height in predicting dyspnea may in fact be due to sex. The fact that in a large proportion of women dyspnea was the chief complaint, whereas only a few of them did not complain of this symptom (Table 2), supports the notion that sex plays a significant role in dyspnea. Furthermore, the similarity of the two final models in their respective contribution to the variance of dyspnea scale (Table 8) underlies the importance of sex in predicting dyspnea (34, 35). This finding is consistent with previous observations that women complain of dyspnea more frequently than do men (34). Moreover, we found that on average, women had a higher degree of dyspnea scale than did men, despite their higher $FEV_1$ (% pred) (Table 1). Although the slope of the regression between dyspnea scale and $FEV_1$ (% pred) was almost the same in men and women, the intercept was higher in the latter (Figure 5). This is consistent with previous observations, and it may be explained by sex differences in the perception of respiratory stress (35).

The sensitivity analysis (Tabel 9) underlines the major role of flow limitation in accurately assessing the intensity of chronic dyspnea. By considering dyspnea scale as gold standard, we found that the five-point FL score is almost as sensitive as $FEV_1$ (% pred) but much more specific. The similarity in sensitivity between the five-point FL score and $FEV_1$ (% pred) implies that the probability for a patient with COPD and dyspnea to have flow-limitation is as high as having a low $FEV_1$ (% pred). The same holds true for severe dyspnea scale. However, the marked discrepancy in specificity between the five-point FL score and $FEV_1$ (% pred) implies that the probability for a patient with COPD without dyspnea not having flow limitation is very high, whereas this is not the case in terms of ventilatory impairment. The same holds for less severe dyspnea scale. Thus, the five-point FL score showed high sensitivity as well as high specificity at both cutoff points compared with $FEV_1$ (% pred), which showed high sensitivity but very low specificity. Accordingly, assessment of FL with the five-point score appears to provide an index that is more closely related to the severity of dyspnea scale than $FEV_1$.

The low specificity of $FEV_1$ (% pred) may be due to the fact that almost half of the patients who were not flow-limited had severe-to-very-severe ventilatory impairment as assessed with $FEV_1$ ($FEV_1 < 49\%$) (Figure 3). These findings imply that $FEV_1$, FVC, and $FEV_1/FVC$ (% pred) are poor predictors of flow limitation, as previously discussed in detail (15). Therefore, the routine lung function tests do not correlate with dyspnea scale as well as either the FL, % $V_T$ index (Table 7) or the five-point FL score. These results, together with the sensitivity analysis, may help to explain at least in part "the failure of routine spirometry measurements to predict dyspnea" (1).

In summary, we found that in patients with COPD (*1*) the correlation of dyspnea scale with a new index of flow limitation (five-point FL score) was stronger ($r_s = 0.73$) than with routine spirometric lung function data ($r_s < -0.4$); (*2*) in multiple regression analysis the five-point FL score remained the best predictor of dyspnea scale even after adjusting for $FEV_1$ (% pred), which was not the case for $FEV_1$ itself; (*3*) the five-point FL score was almost as sensitive as $FEV_1$ (% pred) but much more specific in accurately assessing the severity of dyspnea scale. It should be noted, however, that we do not know if the dynamic airway compression associated with flow limitation per se elicits dyspnea, or is the dyspnea caused by the fact that expiratory flow limitation induces dynamic hyperinflation with concomitant increase of inspiratory muscle activity, functional impairment of inspiratory muscle, etc. Thus, the precise neurosensorial nature of the close association between dyspnea scale and degree of flow limitation found in this study remains as yet to be explained.

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