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How to interpret reduced forced expiratory volume in 1 s (FEV_1)/vital capacity ratio with normal FEV_1

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ABSTRACT: The aim of the present study was to determine whether the combination of low forced expiratory volume in 1 s (FEV_1)/vital capacity (VC) ratio with normal FEV_1 represents a physiological variant or a sign of early airflow obstruction.

We studied 40 subjects presenting with low FEV_1/VC, but FEV_1 within the range of normality predicted by European Respiratory Society reference equations, and 10 healthy controls. All subjects completed two questionnaires and underwent comprehensive pulmonary function testing, which included methacholine challenge and single-breath nitrogen wash-out.

According to the questionnaires, the subjects were assigned to three groups, *i.e.* rhinitis (n=8), bronchial asthma (n=13) and chronic obstructive pulmonary disease (COPD; n=12). Subjects with negative responses to questionnaires were assigned to an asymptomatic group (n=7). Airway hyperresponsiveness was found in four subjects of the rhinitis group, all of the asthma group, and 10 of the COPD group; in the last two groups, it was associated with signs of increased airway closure and gas trapping. Bronchodilator response to salbutamol was positive in only a few individuals across groups. In the asymptomatic group, no significant functional changes were observed, possibly suggesting dysanaptic lung growth.

In subjects with low FEV_1/VC and normal FEV_1, questionnaires on respiratory symptoms together with additional pulmonary function tests may help to clarify the nature of this pattern of lung function.

KEYWORDS: Atopic rhinitis, bronchial asthma, chronic obstructive pulmonary disease, dysanaptic lung growth, methacholine challenge, single-breath nitrogen wash-out

The assumption that a decrease in forced expiratory volume in 1 s (FEV_1) and its ratio to vital capacity (VC) below the fifth percentile of the predicted normal value indicates an obstructive pulmonary abnormality is a useful simple approach [1]. However, in some individuals with VC normal or higher than normal, the FEV_1/VC ratio may lie below the normal range while the FEV_1 is still above the lower limit of normality [2–5]. Whether this spirometric pattern represents a physiological variant, possibly due to dysanaptic lung growth [6–8], or an early sign of airflow obstruction, possibly due to increased airway resistance [9] or loss of elastic recoil [10], is unknown. As the treatment of obstructive pulmonary diseases is based on proper recognition of airflow obstruction [11, 12], the interpretation of this functional pattern is of practical relevance.

The present study was designed to investigate whether a careful assessment of respiratory symptoms, combined with tests sensitive to abnormalities of airway function, may help to interpret the pattern of low FEV_1/VC ratio with normal FEV_1. For this purpose, 40 subjects were studied who presented with an FEV_1/VC ratio below and an FEV_1 above their lower limits of normality according to the European Respiratory Society (ERS) predicting equations [13]. Symptoms were assessed by questionnaires and lung function by additional tests, including measurement of lung volumes, single-breath diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$), bronchodilator response to salbutamol, methacholine (MCh) bronchial challenge and single-breath nitrogen wash-out (SBN_2W-O).

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MATERIALS AND METHODS

Subjects

Forty consecutive Caucasian subjects presenting with an FEV1/VC ratio below the lower limit of normality and FEV1 within the ERS predicted normal range [13] were recruited from 1,386 workers (1,136 males and 250 females, 76% white-collar workers) referred to the Unit of Preventive and Occupational Medicine of San Martino University Hospital (Genoa, Italy) to be spirometrically tested for pre-employment or surveillance purposes. Of the remaining subjects, 1,269 showed a normal spirometry, 72 an obstructive and five a restrictive abnormality confirmed by lung volume measurements. None of the 40 subjects suffered from known cardiopulmonary or systemic diseases. 10 healthy volunteers with both FEV1/VC and FEV1 within the normal range were recruited from the hospital staff to serve as control group. The study was approved by the institutional ethics committee of San Martino University Hospital and written informed consent was obtained prior to the study.

Study design

At the first visit, the selected subjects completed two questionnaires (see online supplementary material). One was administered by an occupational physician and focused on work-related air pollution [14] and habitual physical activity [15]; the other was self-administered and focused on symptoms of atopic rhinitis, bronchial asthma [16, 17] and chronic obstructive pulmonary disease (COPD) [18]. A total score was computed for each disease by grading symptoms according to their temporal frequency. Grading ranged from 0 to 30 for asthma, 0 to 6 for COPD and 0 to 9 for atopic rhinitis, with the higher numbers indicating higher frequency. Control subjects (with normal FEV1/VC ratio and FEV1) showed a total score equal to zero for all the three sections of the self-administered questionnaire. Subjects with a score $\leqslant 2$ for all questionnaire sections were assigned to an asymptomatic group, subjects with a score $\geqslant 3$ for asthma to an asthma group, smokers $\geqslant 20$ pack-yrs and a score $\geqslant 3$ for COPD to a COPD group, and subjects with scores $\geqslant 3$ for rhinitis but <3 for asthma and COPD to a rhinitis group.

Absolute lung volumes and spirometry were measured before and after inhaling 400 μg of salbutamol through a valved-holding chamber [19]. Approximately 1 week after the first visit, the subjects underwent a bronchial challenge with MCh.

Lung function measurements

Standard spirometry was obtained by a mass flowmeter (VIASYS-SensorMedics Inc., Yorba Linda, CA, USA) with numerical integration of the flow signal [19]. $D_{L,CO}$ was measured (Vmax22D; VIASYS-SensorMedics Inc.) at least in duplicate [20].

Absolute lung volumes were measured by a transmural whole-body plethysmograph (V62J; VIASYS-SensorMedics Inc.) [21]. Following thoracic gas volume measurement, the subjects resumed regular breathing and performed a forced expiration from ~70% forced vital capcity (FVC; partial expiratory manoeuvre). Soon after and without disconnecting from the circuit, they took a fast deep breath to total lung capacity (TLC) and, without hesitation, performed a maximal forced expiratory manoeuvre of $\geqslant 6$ s until a flat volume-time plateau was achieved (maximal expiratory manoeuvre) [22, 23]. Then, without coming off the mouthpiece, they resumed tidal breathing and performed a slow inspiratory VC (IVC) manoeuvre. From this set of manoeuvres functional residual capacity, TLC, residual volume (RV), and maximal (V'_{max}) and partial (V'_{part}) forced expiratory flows at 40% control FVC were measured (fig. 1) [24]. The reported value of FEV1/VC is the one calculated by using the largest of the technically acceptable IVCs or FVCs [19].

An SBN_2W-O test [25] was performed by using a Vmax22D (VIASYS-SensorMedics Inc.). After at least four regular breaths, the subjects were asked to fully expire to RV and then to take an IVC of 100% oxygen. This was followed, without breath-hold, by a full expiration to RV at a rate of 0.30–0.50 $L \cdot s^{-1}$. Expiratory nitrogen concentration was plotted against VC and the slope of nitrogen alveolar plateau (phase III) calculated by drawing the best-fit line. The first departure from this straight line exceeding cardiogenic oscillations was taken as the onset of phase IV. The open capacity (OC) was calculated as the difference between TLC and the volume at which phase IV (closing capacity) began [26]. The slope of phase III and OC were measured at least in triplicate, and the mean value retained for analysis. The results were expressed as % predicted (% pred) [25].

MCh challenge

Aerosols of MCh chloride solutions (0.2%, 1% and 6%) were delivered *via* a DeVilbiss 646 nebuliser attached to a KoKo (Rosenthal–French) breath-activated dosimeter (Ferraris, Louisville, CO, USA). Aerosols were inhaled during quiet tidal breathing in the sitting position [27]. Increasing doses of MCh from 40 to 4,800 μg were inhaled until a decrease of FEV1 $\geqslant 20\%$ from control was achieved. FVC, FEV1, V'_{max} and V'_{part} were measured only once at each step to avoid the effects of full lung inflation on airway calibre. The provocative dose of MCh causing an FEV1 decrease of 20% (PD_{20}) was determined by interpolating between two adjacent points of the log dose–response curve. If the FEV1 decrease was $<20\%$ of control, the

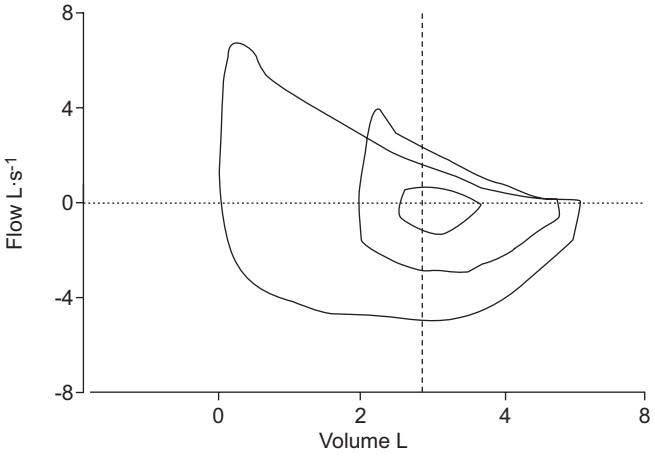

FIGURE 1. Representative tidal, partial and maximal flow–volume curves at baseline in a subject with low forced expiratory volume in 1 s (FEV1)/vital capacity ratio and normal FEV1. ------: 40% forced vital capacity indicating the point where instantaneous maximal and partial expiratory flows were measured.

last dose (4,800 μg) was retained as PD_{20}. The extent of gas trapping during induced bronchoconstriction was estimated from slope and *y*-intercept of the simple regression analysis of all FVC values plotted against the corresponding FEV_1 values [28, 29]. The effects of deep inspiration (DI) during constriction were estimated by the slope and *y*-intercept of simple regression analysis of V'_{max} values plotted against the corresponding V'_{part} values [23]. As opposed to the V'_{max}/V'_{part} ratio, the regression of V'_{max} *versus* V'_{part} is independent of thoracic gas compression volume [30].

Statistical analysis

PD_{20} values were log-transformed before analysis. Data are presented as mean±SD. A generalised linear model was used for comparisons of the data between the 40 subjects with a low FEV_1/VC ratio and normal FEV_1 and controls.

A mixed between-within-groups ANOVA with Duncan's *post hoc* comparisons was used to assess the significance of differences between categories of subjects with abnormally low FEV_1/VC and controls. Chi-squared and Fisher's exact test were used in the analysis of categorical data. Values of $p<0.05$ were considered statistically significant.

RESULTS

Baseline condition

The main anthropometric and life-style parameters were not significantly different between the whole group (n=40) with a low FEV_1/VC ratio and normal FEV_1, and the control group. In the former, the % pred FEV_1 and $D_{L,CO}$ were slightly less than in controls (98±11% *versus* 113±9%, $p<0.001$; and 105±19% *versus* 118±11%, p=0.048, respectively).

Based on questionnaires, only seven subjects with a low FEV_1/VC ratio and normal FEV_1 did not reach the pre-set minimum threshold of symptoms score to be considered abnormal and were included in the asymptomatic group (table 1). Of the remaining 33 subjects, eight were assigned to the rhinitis group, 12 to the bronchial asthma group and 13 to the COPD group. Of the 13 subjects assigned to the COPD group, 12 had also a score of 3 for asthma, but the COPD score was prevalent. Four subjects from the asthma group and five subjects of the COPD group also had positive rhinitis scores.

Anthropometric characteristics, life-style habits, work-related airborne irritants, or aerobic physical activity were similar between groups. The FEV_1 % pred was slightly, though significantly, less (ranging from 102±7% to 97±12%, p=0.006) than in the control group (113±9%), while all other spirometric parameters were not significantly different (p=0.61 and p=0.81 for IVC and FVC % pred, respectively; table 2). The RV/TLC ratio in COPD group was slightly, but significantly, higher (0.34±0.06, $p<0.001$) than in any other group. The slope of phase III was significantly (p=0.001) higher (207±97%) in COPD than in other groups, whereas OC was less in both asthma and COPD (94±8 and 90±8%, respectively, p=0.011), thus suggesting a greater tendency for airway closure (fig. 2).

Bronchodilator response

On average, the FEV_1, IVC, FVC and lung volumes remained unchanged after inhaling salbutamol in all groups. Exceptions were observed in one subject of the control and asymptomatic groups, two of the asthma group, and three of the COPD group, in whom the FEV_1 increased by >12% and 200 mL of baseline. Interestingly, the FEV_1/VC ratio was normalised after salbutamol in four subjects from each of rhinitis, asthma and COPD groups, and in two of the asymptomatic group. Post-bronchodilator changes in V'_{max} were not significantly different among groups (p=0.91), whereas V'_{part} % showed a tendency (p=0.070) to increase more after salbutamol in rhinitis (56±29%) and asthma (64±52%) groups of subjects as compared with those in the COPD group (30±41%).

MCh challenge

At the second visit, the FEV_1/VC at presentation was still below the normal range in all subjects, thus confirming the repeatability of the parameter. All subjects of the asthma group

TABLE 1 Main anthropometric, life-style parameters and symptoms of the groups of subjects

Parameters	Control group	Asymptomatic	Rhinitis	Asthma	COPD
Subjects n	10	7	8	12	13
Age yrs	45±12	45±17	34±6	36±14	57±9
Sex M/F n	8/2	7/0	8/0	11/1	7/6
Height cm	171±8	175±8	178±5	172±8	168±12
BMI kg·m^{-2}	23±2	25±3	24±3	24±3	26±3
Smoking habit pack-yrs	3±4	3±4	4±5	1±4	35±9***
Work-related airborne irritants score=2	0	2	2	2	2
Aerobic physical activity score=2	8	2	6	7	3
Symptoms score range					
Rhinitis	0–0	0–2	4–9	1–8	0–9
Bronchial asthma	0–0	0–2	0–3	4–18	3–18
COPD	0–0	0–0	0–1	0–1	4–6

Data are presented as means±SD or absolute numbers of subjects for work-related airborne irritants, aerobic physical activity, and range of symptoms score, unless otherwise indicated. COPD: chronic obstructive pulmonary disease; M/F: male/female; BMI: body mass index. Comparisons were made using the ANOVA or Chi-squared test (exact Fisher's test). ***: $p<0.001$ *versus* all other groups.

TABLE 2 Main spirometric and volumetric data of the five groups of subjects

Parameters	Group					ANOVA p-value
	Control	Asymptomatic	Rhinitis	Asthma	COPD	
IVC % pred	118±13	120±16	118±13	122±14	126±14	0.61
FVC % pred	118±15	122±19	120±7	124±16	126±14	0.81
t_{FE} s	8.5±2.1	9.7±3.4	9.1±1.7	9.0±1.9	12±4	0.080
FEV_1 % pred	113±9$^{\#,\P,+,\S}$	98±14$^{\#}$	102±7¶	100±12^{+}	97±12§	0.006
ΔFEV_1 %	4±7	8±4	6±3	11±6	8±7	0.082
FEV_1/VC	0.77±0.05$^{\#,\P,+,\S}$	0.64±0.05$^{\#}$	0.67±0.02¶	0.63±0.04^{+}	0.60±0.05§	<0.001
V'_{max} L·s^{-1}	1.80±0.58	1.70±0.60$^{\#}$	2.31±0.60$^{\#,\P}$	2.02±0.67	1.03±0.28¶	<0.001
$\Delta V'_{max}$ %	31±50	32±8	19±9	26±18	28±18	0.91
V'_{part} L·s^{-1}	2.44±0.85	1.95±0.65	2.43±2.34	2.09±0.76	1.60±0.70	0.15
$\Delta V'_{part}$ %	37±39	37±50	56±29	64±52	30±41	0.070
TLC % pred	108±10	112±11	112±9	115 ±13	116±7	0.38
FRC % pred	98±17	105±23	109±21	107±17	109±18	0.68
RV % pred	91±18	100±12	94±21	100±29	111±18	0.24
RV/TLC	0.26±0.05$^{\#}$	0.27±0.07¶	0.22±0.05^{+}	0.24±0.06§	0.34±0.06$^{\#,\P,+,\S}$	<0.001
$D_{L,CO}$ % pred	118±11	104±9	106±15	112±28	99±14.6	0.14
$V_{A,sb}/V_{A,plethys}$	0.99±0.09	0.92±0.06	0.96±0.07	0.93±0.07	0.92±0.07	0.096

Data are presented as mean±SD, unless otherwise indicated. COPD: chronic obstructive pulmonary disease; IVC: slow inspiratory vital capacity; % pred: % predicted; FVC: forced vital capacity; t_{FE}: forced expiratory time; FEV_1: forced expiratory volume in 1 s; ΔFEV_1: percentage change from baseline FEV_1 30 min after inhaling 400 μg of salbutamol; VC: vital capacity; V'_{max}: maximal forced expiratory flow measured at the same absolute lung volume at 40% of baseline FVC; $\Delta V'_{max}$: percentage change from baseline V'_{max} 30 min after inhaling 400 μg of salbutamol; V'_{part}: partial forced expiratory flow measured at the same absolute lung volume at 40% of baseline FVC; $\Delta V'_{part}$: percentage change from baseline V'_{part} 30 min after inhaling 400 μg of salbutamol; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; $D_{L,CO}$: single-breath diffusing capacity of the lung for carbon monoxide; $V_{A,sb}/V_{A,plethys}$: single-breath alveolar volume/plethysmographic alveolar volume ratio. $^{\#,\P,+,\S}$: statistically significant differences between groups by Duncan's *post hoc* analysis. Statistical details are presented in the Results section.

had a cumulative PD_{20} <800 μg (range 31–300 μg) consistent with airway hyperresponsiveness (fig. 3). This was also observed in four subjects with rhinitis and 10 with COPD. In the latter, the slope of FVC *versus* FEV_1 was significantly >1 (p=0.048) and steeper (1.24±0.40, p=0.002) than in any other groups (fig. 4), suggesting that all of the fall in FEV_1 was due to the decrease in FVC, *i.e.* to trapping of air. Moreover, the *y*-intercept was lower (1.19±0.82, p=0.013) than in asymptomatic and rhinitis groups. Similarly, the *y*-intercept of V'_{max} *versus* V'_{part} in COPD was lower (0.28±0.14, p=0.006) than in the control and rhinitis groups, suggesting a reduced bronchodilator effect of DI.

DISCUSSION

The present study was conceived to investigate whether a low FEV_1/VC ratio with an FEV_1 within the predicted normal range may represent a physiological variant or an early sign of obstructive abnormalities. Our findings suggest that routine lung function tests are of little help to resolve this issue. In contrast, in most (33 out of 40) of these individuals, the use of clinical questionnaires of symptoms with additional tests of airway mechanics, such as bronchodilator and bronchoconstrictor responses and SBN_2W-O, revealed abnormalities consistent with early airflow obstruction. In the remaining few subjects (seven out of 40), who were classified as asymptomatic by respiratory questionnaires, the results of additional lung function tests were within normal ranges and indistinguishable from those of the control group, except for a borderline airway hyperresponsiveness to MCh in one subject with a symptoms score of zero.

In agreement with current guidelines [11, 12], an obstructive respiratory disease is diagnosed when symptoms are confirmed by appropriate functional tests. If, in theory, such a statement is sound and represents the basis of our daily clinical practice, things may be not so straightforward when the disease is at its initial stage and/or the functional tests show borderline values. This is exactly the case in our study. In an attempt to shed light on this problem, we combined the results of clinical questionnaires with additional pulmonary function tests.

As for the choice of the functional tests, we used lung volumes, $D_{L,CO}$, and the response to the bronchodilator and bronchoconstrictor agents. The latter was slightly modified to examine the response of the airways to DI, as repeatedly reported in bronchial asthma [31, 32] and COPD [22, 23, 33]. We also included the SBN_2W-O by virtue of its high sensitivity to detect inhomogeneous distribution of ventilation [34].

The $D_{L,CO}$ measurements did not reveal any significant differences between groups with low FEV_1/VC ratio. The MCh challenge documented the presence of airway hyperresponsiveness in all subjects with a history of bronchospasm, thus confirming the results of the questionnaire. Surprisingly, however, we did not see significantly different responses to the DI in these asthmatics, as previously reported [31, 32]. In an

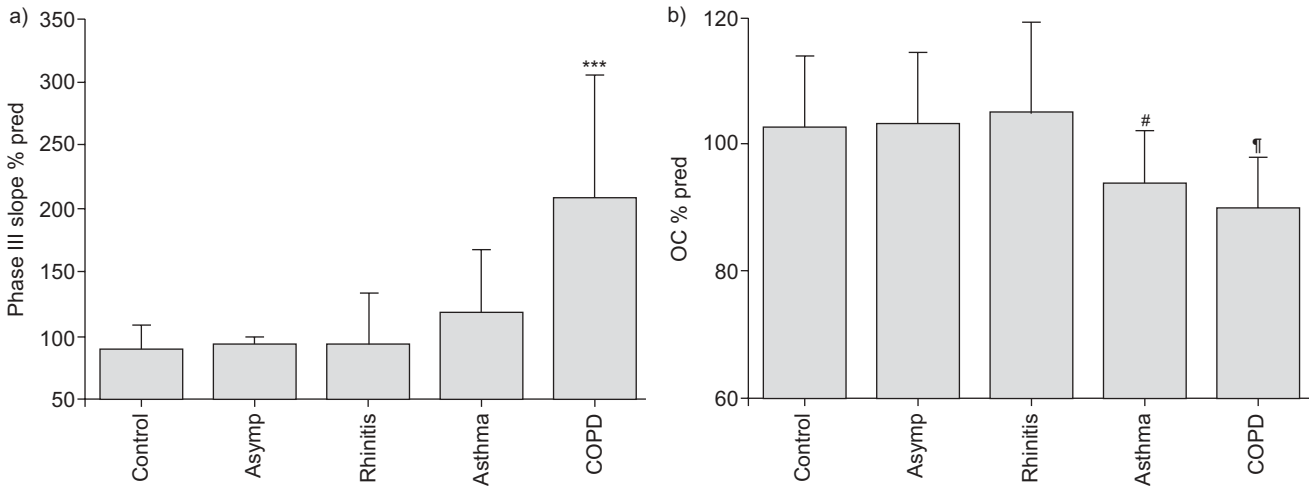

FIGURE 2. Slope of a) phase III and b) open capacity (OC) as % predicted (% pred) of the single-breath nitrogen wash-out. Asymp: asymptomatic; COPD: chronic obstructive pulmonary disease. #: p=0.011 *versus* rhinitis; ¶: p=0.011 *versus* control, asymptomatic and rhinitis; ***: p=0.001 *versus* all other groups.

attempt to explain such an unexpected finding, we postulate that at the transition from health to disease, and with normal or near normal lung function, the bronchodilator effect of DI may still be preserved [31, 32]. In COPD, we observed a high rate of airway hyperresponsiveness and evidence of increased airway closure with gas trapping both at rest (increased RV/TLC and decreased OC) and after exposure to MCh (increased slope and decreased *y*-intercept of the FVC *versus* FEV_1 regression), as well as signs of impaired bronchodilation either with salbutamol (low ΔFEV_1 and $\Delta V'_{part}$ as % of control) or DI during the bronchial challenge (reduced *y*-intercept of the V'_{max} *versus* V'_{part} regression). With the assumption that these subjects were properly assigned to the COPD group, our findings would suggest that increased airway closure with gas trapping and impaired response to large inflation or bronchodilator agents are already part of the early stages of the disease [22, 23].

Finally, we observed an increase in airway responsiveness in about half of the rhinitis group with no other functional alterations. This is consistent with the early stages of asthma being associated with an increased response to a constrictor agent without necessarily causing respiratory symptoms [35].

No abnormalities were observed in functional tests in the group with a low FEV_1/VC ratio but normal FEV_1 and without any history of respiratory diseases or symptoms, except for one subject in whom the response to MCh and salbutamol was slightly abnormal. If our examination reasonably excludes the presence of early obstructive lung diseases in these subjects, it does not help to explain the pattern observed. For instance, we could not see any differences between the control group for sex, age, height, body mass index, occupation and exercise activity. The pattern may have been caused by an asynchronous development of airways and air spaces during the early stages of life, as previously described as dysanaptic lung growth [6–8]. That is, in some individuals, during growth, the lung parenchyma could increase disproportionately to the airways as a result of various natural events or disease conditions occurring before definite maturation of the respiratory system.

As for the rhinitics with increased airway responsiveness, the functional pattern could have been caused by an imbalance between increased force generation capacity of the airway smooth muscle [35] and basal membrane thickness as a result of persistent allergen exposure [36]. Even though this is likely to be part of a remodelling process, there is no evidence suggesting that this might be a risk factor for exaggerated lung function decline. As for the rhinitics with normal response to MCh, the pattern could have been due to the same mechanisms discussed for the asymptomatic subjects. In fact, six out of eight subjects of rhinitis group may have been undergoing an excessive exercise-induced stress or strain imposed on the alveolar septa during growth [37].

The clinical interpretation of the reduced FEV_1/VC ratio and normal FEV_1 in the asthma and COPD subjects appears to be

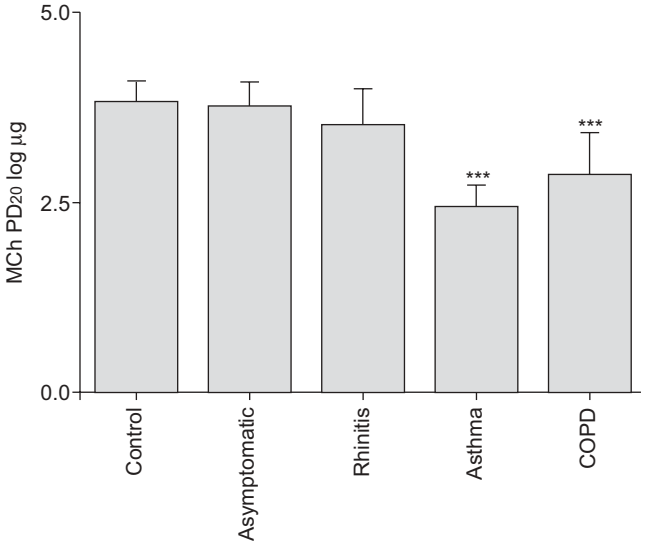

FIGURE 3. Mean ± SD of log-transformed dose of methacholine causing a 20% decrease of forced expiratory volume in 1 s (MCh PD_{20}). COPD: chronic obstructive pulmonary disease. ***: p<0.001 *versus* all other groups.

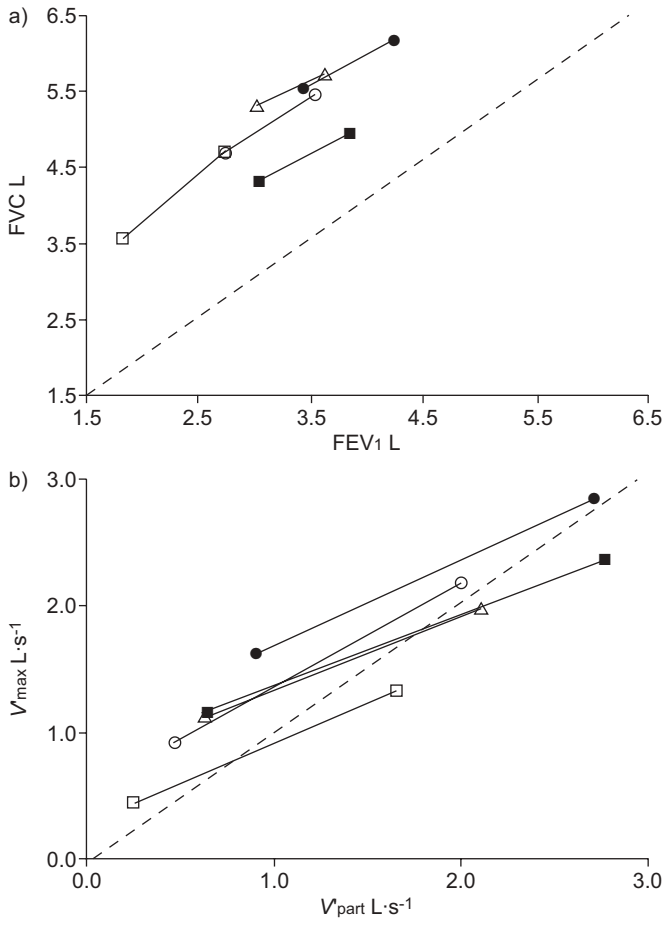

FIGURE 4. Mean linear regression analysis of a) absolute values (L) of forced vital capacity (FVC) *versus* forced expiratory volume in 1 s (FEV_1) and b) of instantaneous maximal ($\dot{V}_{max}$) and partial ($\dot{V}_{part}$) flows ($L \cdot s^{-1}$) at 40% of control FVC at each step of methacholine challenge in the five groups. By regressing FVC against FEV_1 values, an increase of slope or a decrease of *y*-intercept suggests enhanced gas trapping and *vice versa*. Similarly, an increase of slope or a decrease of *y*-intercept of $\dot{V}_{max}$ *versus* $\dot{V}_{part}$ values suggests a reduced bronchodilator effect of deep inspiration. ■: control; △: asymptomatic; ●: rhinitis; ○: asthma; □: chronic obstructive pulmonary disease. -----: line of identity. See text for statistical differences among groups.

more complicated. Under these conditions, the possibility exists that the decrease in FEV_1 was a sign of accelerated decline in lung function in subjects with initial spirometric values higher than normal. In smokers, CORBIN *et al.* [10] found a significant increase in TLC and VC due to loss of lung elastic recoil, while FEV_1 only tended to decrease, thus resulting in a decrease in FEV_1/VC preceding the decrease of FEV_1. In the absence of pressure–volume measurements, we can only speculate that this mechanism might have contributed to our findings in the COPD group.

We recognise that our study has some limitations. First, we used the predicting equations published by the European Respiratory Society [13, 38], mainly because they are still the most frequently used in Europe [1]. The values of VC and FEV_1 obtained in our control group were mostly >100% pred, suggesting that the predicted values were somehow underestimated. Supposedly, the use of different reference equations might have resulted in an FEV_1 falling below normal range in some of our subjects, thus leading to a diagnosis of airflow obstruction without qualification. When predicted values were recalculated using predicting equations recently derived from a large Caucasian-American population [39] and a local population of northern Italy [40], only one subject from the COPD group had an FEV_1 slightly below the lower limits of normality (9 and 6%, respectively). Exclusion of this subject did not abolish the significance of differences between groups. Secondly, we used questionnaires that had already been validated [14–18], but a cut-off of more than two for positive responses was arbitrarily chosen. This was done to seek for high specificity, but could have resulted in a low sensitivity. However, only one subject assigned to the asymptomatic group had a symptom score for asthma of two, but the disease was reasonably excluded by a lack of response to MCh. Thirdly, there were overlaps of either symptoms or lung function, particularly between the asthma and COPD groups, but this does not invalidate the conclusion that the low FEV_1/VC ratio in these subjects may be a marker of airflow obstruction, despite FEV_1 still being normal.

In summary, in subjects with a reduction of FEV_1/VC as the only spirometric abnormality, lung volume measurement, reversibility or challenge tests, SBN_2W-O and appropriate questionnaires may help to assist in detecting an early obstructive abnormality. In the case of positive history for bronchial asthma and significant responses to bronchodilator and/or bronchoconstrictor agents or in heavy smokers with signs of airway closure either at baseline or after induced bronchoconstriction, the pattern is highly suggestive of airflow obstruction. By contrast, in subjects with rhinitis or no respiratory symptoms, and normal or slightly increased bronchodilator or bronchoconstrictor responses, the pattern is presumably due to either initial airway remodelling or dysanaptic lung growth.

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