Reduced FEV_1/FVC and FEV_1 in the Normal Range as a Physiological Variant

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BACKGROUND: Healthy individuals without respiratory symptoms can sometimes present with low FEV_1/FVC. The objective of this study was to characterize and compare subjects without symptoms and with reduced FEV_1/FVC but normal FEV_1 with subjects with mild obstructive lung disease. METHODS: Fifty healthy subjects with FEV_1/FVC below the fifth percentile of reference values (normal variants) were compared with 52 subjects with asthma and 48 subjects with COPD who had similar FEV_1/FVC. RESULTS: Subjects without symptoms were more likely to be male, younger, and taller, and to have higher FVC%, FEV_1%, mid expiratory flow, and terminal flow than subjects with obstructive disease. A receiver operating characteristic curve analysis determined that the best separation between the groups was provided by age < 55 y, height ≥ 167 cm, and FVC > 105%. A logistic regression analysis confirmed that male sex, age, FVC%, and FEF_{75} (Forced expiratory flow in 75% of forced vital capacity) were significant factors for discriminating subjects without symptoms from those with obstructive lung disease. CONCLUSIONS: A reduced FEV_1/FVC may be a normal finding in younger-to-middle age male subjects with an FVC% value above the mean predicted value, especially when terminal flow is within the normal range. *Key words: airway obstruction; asthma; chronic obstructive pulmonary disease; expiratory flow; lung function; lung functions testing; spirometry.* [Respir Care 2019;64(5):570–575. © 2019 Daedalus Enterprises]

Introduction

The diagnosis of obstructive lung disease can be made based on an FEV_1/FVC below the fifth percentile of the predicted value,[1] and the diagnosis is reinforced by observed reductions in both FEV_1 and the FEV_1/FVC. Physicians must be cautious when interpreting obstructive dysfunction from an FEV_1/FVC below the lower limit of normal when FEV_1 and FVC are both higher than predicted values because this pattern is sometimes seen in healthy subjects.[2] Smokers ages ≥ 40 y with a history of ≥20 pack-years of smoking have a higher risk for COPD. In these patients, a reduced FEV_1/FVC has a high predictive value for diagnosis.[3,4] In healthy individuals without respiratory symptoms, a finding of a low FEV_1/FVC with normal FEV_1 has been posited as a physiological variant of normal.[5]

In adults, the FEV_1/FVC decreases with increased stature in both sexes.[6] In males with a tall stature, FEV_1/FVC can be lower than expected.[7] Muscular force is greater in younger males with a taller stature and higher FVC values, which potentially cause decreased FEV_1 as a result of inverse effort dependence.[8] Mid and terminal expiratory flows are less effort dependent than FEV_1 and FVC, and are reduced in the early stages of diffuse obstructive diseases, such that they may be helpful for differentiating normal variants from patients with spirometric obstructive defects. The aim of this study was to identify factors that separate healthy subjects with reduced FEV_1/FVC from subjects with mild obstructive lung disease.

Methods

This was a prospective observational study of 150 subjects who visited 1 of 3 pulmonary function laboratories at

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2 centers in São Paulo, Brazil. Spirometric testing was performed as part of an annual physician visit or a lung function assessment of several employers. The study was approved by the ethics committees of both participating centers. All the subjects completed an epidemiologic respiratory questionnaire, which was previously translated and validated in Brazil.[9] Spirometric tests were administered by certified technicians in accordance with the Brazilian Thoracic Society criteria.[4] Based on this guideline, the highest value of FEV_1 was selected from the 3 best curves, with peak expiratory values > 90% of the highest value. All the subjects were white and had age and height in the range of values used for the derivation of the reference values.[6]

All the subjects had a mildly decreased FEV_1/FVC (below the fifth percentile of the predicted value, but >80% of the predicted value) and FEV_1 and FVC values within the normal range. The subjects were classified into 3 groups after review of the questionnaire responses: (1) normal variant, characterized by healthy non-smokers without present or past respiratory or cardiovascular disease, or any condition that could result in abnormal lung function; (2) asthma–non-smokers, with a current or past physician diagnosis of asthma with compatible symptoms as indicated by the questionnaire (≥2 attacks of wheezing relieved by a bronchodilator); and (3) COPD-smokers, characterized by a physician diagnosis of COPD, a smoking history of >20 pack-years, and compatible symptoms as indicated by the questionnaire (the presence of chronic cough and/or dyspnea).

The sample size was estimated by using the variation in FVC values from the first 20 subjects included in each group because didn't have any previous studies to analyse the same data of this study. The analysis indicated that 40 subjects per group were sufficient to allow separation with $\alpha < 0.05$ and $\beta > 0.8$. Normality of the data were evaluated by using the Kolmogorov-Smirnov test. Age, stature, and functional variables were adjusted to normal curves. Variables were compared among the 3 groups by using an analysis of variance and Tukey post hoc tests. Chi-square and Fisher exact tests were used to analyze categorical data.

A second analysis was performed in which subjects with asthma and COPD were compared with normal variant subjects. Age, height, FVC, and forced expiratory flows cutoff points for separating these 2 groups (one group - subjects with asthma and COPD and the other with normal variant) were calculated by using receiver operating characteristic curves. Finally, a logistic regression was performed for select variables to test the ability to discriminate the normal variant group from the obstructive defect group (both asthma group and COPD group). Data were expressed as mean ± SD. All analyses were performed by using IBM SPSS statistics package version 19.0. A P value of $< .05$ was considered to be statistically significant.

QUICK LOOK

Current knowledge

The diagnosis of obstructive lung disease is based on a reduced FEV_1/FVC. The diagnosis of an obstructive lung defect is usually correct when FEV_1 and FEV_1/FVC are both reduced. One should be cautious in characterizing obstructive dysfunction when the FEV_1/FVC is below the lower limit of normal but FEV_1 and FVC are in the normal range because this pattern is sometimes seen in healthy individuals.

What this paper contributes to our knowledge

This study showed that, in comparison with the subjects with asthma and COPD with mild air-flow obstruction, reduced FEV_1/FVC should be considered as a normal variant in young and non-elderly adults males who are asymptomatic and with FVC above mean predicted values and terminal flows within the normal range.

Results

Of 150 subjects evaluated, 95 were male and 55 were female. Fifty were classified into the normal variant group, 48 into the asthma group, and 52 into the COPD group. Anthropometric and spirometric data for the 3 groups are summarized in Table 1. In terms of absolute values, FEV_1/FVC values were lowest in the COPD group; however, when the values were calculated as percentages of predicted values, there were no notable differences among the 3 groups. There was a larger proportion of male subjects in the normal variant group (86%) compared with the asthma (48%) and COPD groups (56%) ($\chi^2 = 17.26$, $P < .001$).

The subjects in the normal variant and asthma groups were similar in terms of age but were younger than those in the COPD group. A receiver operating characteristic curve analysis revealed that age < 55 y was the best cutoff for separating the normal variant group from the asthma and COPD cohorts (area under the curve, 0.70 [95% CI 0.62–0.78]). In the normal variant group, 88% of the subjects were < 55 y of age compared with 52% of subjects in the obstructive defect group (both asthma group and COPD group) ($\chi^2 = 18.75$, $P < .001$) Mean height was higher in the normal variant group compared with the asthma and COPD groups. A receiver operating characteristic curve analysis revealed that height ≥ 167 cm was the best cutoff for separating the normal variant group from the asthma and COPD groups (area under the curve,

Table 1. Demographic and Functional Data in Normal Variant Group and Subjects With Asthma and COPD

Variable	Normal Variant Group (n = 50)	Asthma Group (n = 48)	COPD Group (n = 52)	P
Age, mean ± SD y	42 ± 10	44 ± 15	61 ± 12	<.001
Male/female, n	43/7	23/25	29/23	<.001
Height, mean ± SD cm	173 ± 9	166 ± 9	165 ± 10	<.001*
Body mass index, mean ± SD kg/m^2	27.0 ± 4.0	27.6 ± 4.4	26.1 ± 3.8	.15
FVC% predicted, mean ± SD	110 ± 10	104 ± 10	102 ± 10	.001*
FEV_1 % predicted, mean ± SD	95 ± 8	90 ± 8	89 ± 9	<.001*
FEV_1/FVC, mean ± SD	0.70 ± 0.02	0.71 ± 0.02	0.68 ± 0.02	<.001*
FEV_1/FVC, mean ± SD %	86 ± 2	87 ± 2	86 ± 2	.56
FEF_{max}, mean ± SD %	84 ± 11	80 ± 12	79 ± 15	.19
FEF_{50}, mean ± SD %	67 ± 10	62 ± 8	60 ± 10	<.001*
FEF_{50} reduced, %	18	35	40	.04†
$FEF_{25-75\%}$, mean ± SD, %	68 ± 10	61 ± 9	57 ± 9	<.001*
FEF_{25-75} reduced, %	16	38	63	<.01
FEF_{75}, mean ± SD, %	71 ± 15	61 ± 12	56 ± 11	<.001*
FEF_{75} reduced, %	22	42	58	.001
FEF_{75-85}, mean ± SD, %	72 ± 20	61 ± 14	58 ± 12	<.001*
FEF_{75-85} reduced, %	18	38	40	.03

* Tukey test: normal variant vs asthma and COPD.
† χ^2 test: normal variant vs asthma and COPD.
FEF_{max} = Peak expiratory flow
FEF_{50} = Forced expiratory flow 50% of CVF
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver
FEF_{75} = Forced expiratory flow 75% of CVF
FEF_{75-85} = Forced expiratory flow Betwen 75–85% of CVF

0.72 [95% CI 0.63–0.80]). In the normal variant group, 80% of subjects had heights ≥ 167 cm compared with 46% of subjects in the obstructive defect group (both asthma group and COPD group) (χ^2 = 15.75, P < .001).

FVC and FEV_1 values were higher in the normal variant group than in the other groups (Table 1). Tukey post hoc tests revealed that this difference was significant between the normal variant and asthma groups and between the normal variant and COPD groups. A receiver operating characteristic curve analysis revealed that FVC > 105% of predicted was the best cutoff for separating the normal variant group from the asthma and COPD groups (area under the curve, 0.70 [95% CI 0.61–0.79]). In the normal variant group, 68% of subjects had FVC > 105% of predicted compared with 35% of the subjects in the obstructive defect group (both asthma group and COPD group) (χ^2 = 14.61, P < .001).

Flows at mid and low lung volumes were higher in the normal variant group than in the other groups (Table 1). A receiver operating characteristic curve analysis revealed that $FEF_{25-75\%}$ and FEF_{75} values had the largest areas under the curve for separating the normal variant group from the asthma and COPD groups (Fig. 1). In the normal variant group, 84% of subjects had an $FEF_{25-75\%}$ value in the normal range compared with 49% of the subjects in the obstructive defect group (χ^2 = 17.11, P < .001). Similarly, 78% of the subjects in the normal variant group had an FEF_{75} value in the normal range compared with 50% of the subjects in the obstructive defect group (χ^2 = 10.83, P < .001).

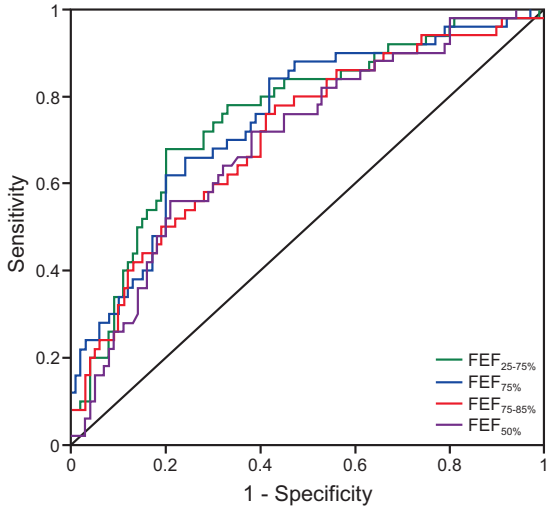

Fig. 1. Receiver operating characteristic curves for mid and terminal flows in normal variant cases and subjects with air-flow obstruction.

A logistic regression analysis confirmed that sex, age, FVC% and FEF_{75} were significant factors for separating the normal variant group from the obstructive defect group (Table 2). Stature and $FEF_{25-75\%}$ were not signif-

Table 2. Adjusted Logistic Regression for Determination of Probability of Normal Variant in Comparison With Subjects With Mild Obstructive Disease (Asthma and COPD)

Variable	Odds Ratio (95% CI)	*P*
Males	10.57 (3.50–31.00)	<.001
Age < 55 y	5.67 (1.91–16.84)	.002
FVC > 105% predicted	4.08 (1.66–10.04)	.002
FEF_{75} reduced	2.79 (1.07–7.30)	.036

Adjusted for height and $FEF_{25-75\%}$.
FEF_{75} = Forced expiratory flow 75% of CVF

icant in this analysis (data not shown). When only males were compared between normal variants ($n = 43$) and subjects with asthma and COPD ($n = 52$), higher values were still found in normal variants (FVC = 109.9 ± 9.6% vs to 102.0 ± 8.3% and FEF_{75} 70.7 ± 16.0% vs 57.8 ± 10.5% of predicted values, $P < .01$ for both comparisons).

Discussion

The present study found that, compared with the subjects with asthma or COPD, normal variant individuals (characterized by a low FEV_1/FVC and FEV_1 in the normal range) were more likely to be male, younger, and have higher FVC and FEF_{75} values in the normal range. Only 2 previous studies evaluated subjects without symptoms and with low FEV_1/FVC, and compared them with a control group or subjects with obstructive disease.[5,10] In the first published study, healthy males who showed reduced FEV_1/VC (FEV_1/vital capacity) were compared with healthy subjects with FEV_1/VC within the normal range and with similar age.[10] Spirometric response to bronchodilators, lung volumes, and bronchial provocation tests were similar between the 2 groups.[10] The second study performed a careful analysis of respiratory symptoms combined with sensitivity tests for detecting airway obstruction in an attempt to separate healthy subjects ($n = 7$) with low FEV_1/FVC from subjects with respiratory disease ($n = 33$).[5] The investigators concluded that routine lung function tests were of little use for separating patients with physiological variants from those with respiratory disease; however, data for mid and terminal flows were not shown.[5] In contrast, most cases with respiratory symptoms show additional abnormalities on sensitive tests of airway mechanics.

There are 2 plausible reasons for the observation of low FEV_1/FVC in healthy subjects: dysanapsis and inverse effort dependence on expiratory flow. The term dysanapsis has been used to reflect physiological variation in the geometry of the tracheobronchial tree and lung parenchyma due to different (unequal) patterns of growth. Mead[11] examined the association between airway size (estimated by using maximal expiratory flow/static recoil pressure at 50% VC) and lung size (estimated by using VC) in adult men and women, and found that airway diameter was, on average, 17% larger in healthy adult men than in women. Additional support for the relevance of dysanapsis to the observation of low FEV_1/FVC in healthy subjects comes from studies that estimated the acoustic reflectance of the tracheal area in healthy young men and healthy adult women. In a subset of subjects matched for total lung capacity, Martin et al[12] found that the tracheal cross-sectional area was 29% smaller in women than in men. More recently, Sheel et al[13] used computed tomography to show that the largest conducting air ways in females are significantly smaller than those in males, even after controlling for lung size. In the present study, the normal variant group was 86% male, which indicated that dysanapsis was not the cause of low FEV_1/FVC in the whole sample.

Several studies showed that submaximal expiratory effort can increase expiratory flows.[14,15] In one critical study, Krowka et al[8] evaluated the difference between the highest FEV_1 observed in expiratory maneuvers with variable effort and FEV_1 from the maneuver with the greatest peak expiratory flow, and found that the difference for FEV_1 was always > 0 with lower degrees of effort; the mean difference in all the sessions was 110 mL.[8] When poorly reproducible maneuvers were excluded from the analysis, this difference decreased to 80 mL but remained significant ($P < .05$).[8] The investigators concluded that, during standard spirometry, FEV_1 is inversely dependent on effort due to the effect of thoracic gas compression on lung volume, and as a result, the investigators recommended the exclusion of FEV_1 values from spirometry maneuvers performed with submaximal effort as indicated by a decrease in peak expiratory flow.[8] In the present study, FEV_1 values were selected from maneuvers with a peak expiratory flow of >90% of the highest value.[4] It is notable that the influence of inverse effort dependence on FEV_1 was greater in patients with obstructive lung disease.

The compressed volume of intrathoracic gas is influenced by alveolar pressure and lung volume, which, in turn, are influenced by a combination and interaction of length-tension and force-velocity relationships in respiratory muscles, lung elastic recoil pressure, lung volume, and airway resistance.[8] Our observation that physiological variants were more likely to be young males with high FVC values can be explained by several possible mechanisms. First, young male subjects generate greater expiratory efforts during forced expiratory maneuvers. A higher FVC indicates an advantage for the expiratory muscles, that is, greater length results in greater force. A high FVC could also be the result of greater force exerted by the inspiratory muscles. In our logistic regression analysis,

FVC but not stature remained significant as a factor that discriminated the normal variant group from the obstructive defect group. This finding indicated that muscle force was the most relevant finding (greater lung gas compression occurred as a result of greater muscular effort), even in male subjects with shorter statures.

Lastly, it is well known that flows at low lung volume are less influenced by respiratory effort than flows at higher lung volumes[16]; therefore, it was expected that flows at low lung volumes would be better preserved (ie, closer to normal) in the normal variant group. Indeed, we found that all mid and terminal flows were preserved when expressed as percentages of the predicted values in the normal variant group compared with the asthma and COPD groups. Maintenance of flows in lower lung volumes can also be explained by higher values of FVC because these flows are dependent on lung volume. In our study, flows in lower volumes were more preserved in comparison with FEV_1/FVC but were not always reduced in cases generally with asthma/COPD. The inclusion criterion was reduced FEV_1/FVC in all the subjects, although to a mild degree. We commonly observed that isolated reduction in terminal expiratory flows can be the only abnormality indicative of air-flow obstruction, usually in patients with FVC values in the lower range of reference values.

The present study had several limitations. We did not perform detailed tests of lung function, such as measurements of slow vital capacity, diffusing capacity of the lung for carbon monoxide, response to bronchodilator, respiratory pressures, and bronchoprovocation tests. However, 2 studies did not show bronchial hyper-responsiveness in normal variant subjects, which indicated that these tests would have yielded normal results.[5,10] Healthy subjects were not re-evaluated after bronchodilator use due to the need for quick consecutive testing in checkup evaluations. Unfortunately, the total number of non-smokers who were asymptomatic and who received routine spirometry was not designed to calculate the prevalence of normal variants.

Muller[7] observed that, in community surveys, many taller subjects could have reduced FEV_1/FVC with FEV_1 within the normal range. The investigator indicated that this could reflect inaccuracies in the regression equations used to predict normal values because relatively few subjects of such great height are included. In the present study, all the subjects had both age and height within the range of reference values. Reference values in Brazilian white male adults were derived from 270 subjects.[6] Of these, 165 were ages $\leq$50 y and, of these, the mean $\pm$ SD was 172.4 $\pm$ 6.9 cm. In 43 male subjects in the normal variant group in the present study, the mean $\pm$ SD age was 42.6 $\pm$ 9.3 y and mean $\pm$ SD height was 175.3 $\pm$ 7.1 cm ($t = 2.44$, $P = .02$). When stature was entered in logistic regression, it became nonsignificant, with FVC% being more relevant.

In the subjects in the normal variant group in the present study, the lower limit for FEV_1/FVC by using Brazilian reference values would be, for a male with the same mean age and stature, 0.74, compared with 0.70 by both Hankinson and Global Lung Initiative (GLI) reference values.[17,18] Hankinson values to predict FEV_1/FVC do not include stature. In GLI equations, there was a very small inverse correlation between stature and FEV_1/FVC. In Brazilian equations, FEV_1/FVC correlated inversely with stature. Compared with the Brazilian reference values, the GLI equations have lower limits for FEV_1/FVC, decreasing its sensitivity for a diagnosis of air-flow obstruction.[19,20] Brazilian equations for spirometry were validated in a second study.[21] The diagnosis of asthma was obtained by questionnaire, with several subjects who reported past diagnoses of asthma, such as during childhood. It is noteworthy that air-flow obstruction and bronchial hyper-responsiveness can persist long after a clinical remission of asthma.[17] Also, the results of the present study should be tested in a validation sample.

Conclusions

Reduced FEV_1/FVC was not necessarily indicative of air-flow obstruction in otherwise healthy adults. The possibility of normal variant status should be considered in patients who are asymptomatic, especially in males $<$ 55 y of age with an FVC above mean values and FEF_{75} values in the normal range.

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