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Original Research

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An Isolated Reduction of the FEV_3/FVC Ratio Is an Indicator of Mild Lung Injury

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Background: **The FEV_3/FVC ratio is not discussed in the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for lung function interpretation in spite of narrow confidence limits of normal and its association with smoking. We sought to determine whether a reduction in only the FEV_3/FVC ratio was associated with physiologic changes compared with subjects with normal FEV_1/FVC and FEV_3/FVC ratios.**

Methods: **Lung volumes and diffusion were studied in individuals with concomitant spirometry. Patients with restriction on total lung capacity (TLC) were excluded, as were repeat tests on the same patient. A total of 13,302 subjects were divided into three groups: (1) normal FEV_1/FVC and FEV_3/FVC (n = 7,937); (2) only a reduced FEV_3/FVC (n = 840); and (3) reduced FEV_1/FVC (n = 4,525).**

Results: **Subjects with only a reduced FEV_3/FVC compared with those with normal FEV_1/FVC and FEV_3/FVC ratios had higher mean % predicted TLC (99.1% vs 97.1%, $P < .001$), residual volume (RV) (109.4% vs 102.3%, $P < .001$), and RV/TLC ratio (110.1% vs 105.4%, $P < .001$). They had lower mean % predicted FEV_1 (82.6% vs 90.2%, $P < .001$), inspiratory capacity (94.5% vs 98.2%, $P < .001$), and diffusing capacity of lung for carbon monoxide (DLCO) (78.3% vs 81.9%, $P < .001$). Their mean BMI was lower (30.8 vs 31.5, $P < .005$), they were older (61.2 vs 57.2, $P < .001$), and more likely male (52.0% vs 40.4%, $P < .001$), with no racial differences. Comparing this group to those with a reduced FEV_1/FVC, similar but greater differences were noted in all of the previous measurements, though mean age and sex were not significantly different.**

Conclusions: **The FEV_3/FVC ratio should be routinely reported on spirometry. An isolated reduction may indicate an early injury pattern of hyperinflation, air trapping, and loss of DLCO.**

CHEST 2013; 144(4):1117–1123

Abbreviations: ATS = American Thoracic Society; DLCO = diffusing capacity of lung for carbon monoxide; ERS = European Respiratory Society; FEF_{25-75} = forced expiratory flow between 25% and 75% of FVC; IC = inspiratory capacity; NHANES III = National Health and Nutrition Examination Survey III; RV = residual volume; SVC = slow vital capacity; TLC = total lung capacity

Over the last half century, there has been a quest to find a sensitive measurement for mild or early airways disease. In 1955, Leuallen and Fowler[1] coined the term mid-flow obstruction, describing flow rates between 25% and 75% of the FVC. Though flow rates of other percentages of the FVC have been described, the most enduring has been the forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}).

In 2006, Hansen et al,[2] using the National Health and Nutrition Examination Survey III (NHANES III) database,[3] created race-adjusted predicted regression equations for the FEV_3/FVC ratio and compared its efficacy for identifying mild airways obstruction against the FEF_{25-75}. They also described its relationship to a

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Manuscript received November 18, 2012; revision accepted February 6, 2013.

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Part of this article was presented in poster form at the American College of Chest Physicians meeting, Atlanta, GA, October 24, 2012.

Funding/Support: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: 10.1378/chest.12-2816

smoking history. They found almost 700 citations for the FEF_{25-75}, but only 22 for the FEV_3 and FEV_3/FVC. Almost all of the FEF_{25-75} studies used observational % predicted values of about 75% to 80% to determine the lower limit of normal. This practice continued even after 1978 when Knudsen and Lebowitz[4] published spirometry predicted data demonstrating the lower 95% limit of normal for the FEF_{25-75} was around the mid-50th percentile of predicted in individuals over 36 years of age. In 1984, the Intermountain Thoracic Society recommended using the FEV_3/FVC and its 95% confidence limits of normal rather than the FEF_{25-75},[5] using the regression equations of Crapo,[6] eliminating the FEF_{25-75} from consideration[1,7,8] because it did not add significantly to the FEV_1/FVC and the FEV_3/FVC.[8,9] Using our institutional pulmonary function laboratory database of >70,000 patients, we compared subjects with no airways obstruction on spirometry to those with an isolated reduction of the FEV_3/FVC to determine whether there were other physiologic differences supporting that this is a finding of not only mild airways obstruction but also an indicator of early lung injury.

Materials and Methods

This study was performed with the permission of the institutional review board for Henry Ford Hospital (Detroit, Michigan; IRB 7341). None of the authors had a conflict of interest to report. Data were collected from a database of pulmonary function tests performed over 10 years by a core group of technicians. A staff pulmonologist read and reviewed all tests daily, as well as testing being monitored by the laboratory supervisor for the purpose of quality control and adhering to the American Thoracic Society (ATS) standards (as delineated later in this section). Patients younger than the age of 20 years were excluded. Race was self-selected from an institutional approved list.

Only Vmax equipment and software were used for testing, though updated software versions were added as the laboratory expanded over the years (Legacy and Spectra versions; CareFusion Corporation). The first test was selected in which a patient had combined spirometry, plethysmography volumes, and diffusion. Testing protocols and calibration adhered to guidelines recommended by the ATS in 1991[10] and later updated by the ATS/European Respiratory Society (ERS) in 2005.[11-14]

For spirometry, only tests that achieved a minimum expiratory time of 6 s were used for this study, taking the effort with the best FEV_1 + FVC. Only predilator spirometry was studied, noting that often postdilator studies were not ordered or not performed because the patient was routinely taking these medications. It is recognized on subsequent testing, patients may have improved with training or after receiving bronchodilators.[15]

Plethysmography was performed using variable pressure technique, calibrating daily according to the manufacturer's guidelines and monthly using biologic controls. The order of expiratory reserve volume and vital capacity maneuvers was adjusted based on the severity of lung disease and degree of dyspnea. Although nitrogen volumes and plethysmography are usually simultaneously performed in our laboratories, for the purpose of this study, we only included patients who had plethysmography performed. If the slow vital capacity (SVC) (obtained during the performance of lung volume measurements) was lower than the FVC, the larger of the values was used for calculating the total lung capacity (TLC).

Diffusion calibration was performed internally prior to each patient test according to the manufacturer, along with using frequent biologic controls. Using a single-breath technique, a minimum of two acceptable efforts was collected with averaging of results. The diffusing capacity of lung for carbon monoxide (DLCO) was corrected for hemoglobin or carboxyhemoglobin whenever recent values were available. Both hemoglobin corrected and uncorrected values are reported with similar results.

Patients were categorized into three groups using NHANES III spirometry 95% lower confidence limits of normal: group 1, normal FEV_1/FVC and FEV_3/FVC; group 2, only FEV_3/FVC reduced; or group 3, FEV_1/FVC reduced.[2,16] Crapo-predicted volumes and their 95% confidence limits of normal (TLC, residual volume [RV], RV/TLC, inspiratory capacity [IC]) were used for whites, and corrected for blacks according to ATS/ERS guidelines ($TLC \times 0.88$, $RV \times 0.93$, and $RV/TLC \times 1.05$).[15,17] Miller nonsmoking predicted equations were used for diffusion and corrected downward 0.93 for blacks.[15,18] The 4% belonging to other races were adjusted according to ATS/ERS guidelines. To adjust for demographic differences in race, sex, age, and height, the % predicted values were compared, although absolute values were also compared with similar results.

The study variables of interest were compared between the three paired groups. For the dichotomized categorical comparison variables (smoker, sex, race), comparisons were made using the χ^2 test for binomial data. Numeric and normally distributed variables were compared using two-sample *t* tests (BMI, weight in kilograms, age, and % predicted FVC, FEV_1, TLC, RV/TLC, IC, and DLCO). Numeric and non-normally distributed variables were compared using the Wilcoxon rank sum test (% predicted RV). The Bonferroni multiple comparison adjusted was used to reduce each test's rejection level for significance from $P = .05$ to $P = .017$. SAS software (version 9.2; SAS Institute Inc) was used to run the statistical analysis.

Results

This discussion will focus on the comparison of the patients without restriction on TLC (based on 95% lower limits of normal). Comparisons will first be made between those who have no evidence of obstruction on spirometry (group 1: FEV_1/FVC and FEV_3/FVC ratios normal), to those with only a reduced FEV_3/FVC ratio (group 2) (Tables 1, 2). Comparisons will then be made between those with only a reduced FEV_3/FVC (group 2), to those that had a reduced FEV_1/FVC (group 3). In Tables 1 and 2, we did not compare the group with normal ratios (FEV_1/FVC and FEV_3/FVC) to those with a reduced FEV_1/FVC (group 1 vs group 3) because the results are what one would expect to find and add nothing to the discussion.

The data are shown in their entirety in Tables 3 and 4. Table 3 is the data set including patients with restriction based on TLC, and Table 4 is after removal of all patients with TLC below the lower limit of normal. The results are similar in both patient populations.

After eliminating patients with restriction on TLC, we had 7,937 patients in our group with no obstruction

Table 1—*Comparison Results for Demographic Data Excluding Subjects With Restriction on TLC*

Variable	Group 1 (n = 7,937) Normal FEV_1/FVC and FEV_3/FVC	Group 2 (n = 840) Only $FEV_3/FVC\downarrow$	Group 3 (n = 4,525) $FEV_1/FVC\downarrow$	*P* Value: Compare Group 1 to Group 2	*P* Value: Compare Group 2 to Group 3
Smoker					
No	6,102 (76.9)	602 (71.7)	3,011 (66.5)	< .001 (C)[a]	.004 (C)[a]
Yes	1,835 (23.1)	238 (28.3)	1,514 (33.5)	…	…
Sex					
Female	4,730 (59.6)	403 (48.0)	2,276 (50.3)	< .001 (C)[a]	.216 (C)
Male	3,207 (40.4)	437 (52.0)	2,249 (49.7)	…	…
Race					
Black	3,116/7,599 (41.0)	329/818 (40.2)	1,619/4,419 (36.6)	.664 (C)	.051 (C)
White	4,483/7,599 (59.0)	489/818 (59.8)	2,800/4,419 (63.4)	…	…

Categorical data are given as fraction (%) of group. (C) = χ^2 test; TLC = total lung capacity.
[a]Statistically significant, $P < .017$.

on spirometry, 840 subjects that only had a reduced FEV_3/FVC, and 4,525 subjects with obstructive spirometry based on the reduced FEV_1/FVC ratio (Table 1).

Table 1 shows the distribution of sex across the study groups. Women were more likely to have no obstruction than men (59.6% vs 40.4%) while the groups with only a reduced FEV_3/FVC compared with those with a reduced FEV_1/FVC were equally distributed between the sexes ($P < .001$). The higher proportion of women represented in the group with no evidence of obstruction on spirometry may in part be explained by there being a greater percentage of women being nonsmokers than men (76.9% vs 23.1%). Because we studied only the first patient test in which there was simultaneous spirometry, volumes, and diffusion, this may not have been the first time testing was performed. It was later discovered that the patient's smoking history obtained during the initial evaluation did not automatically repopulate the demographics field. Though the smoking incidence is underrepresented, the findings of an increased incidence and severity of obstruction in those with a greater smoking history is not unexpected. Table 1 shows that subjects with normal ratios (no obstruction) had a lower incidence of a smoking history than those with only a reduced FEV_3/FVC ratio (23.1% vs 28.3%, $P < .001$). And those with only a reduced FEV_3/FVC ratio had less of a smoking history than when the FEV_1/FVC

Table 2—*Comparison Results for Degree of Obstruction Excluding the Patients With Low TLC*

Variable	Group 1 (n = 7,937) Normal FEV_1/FVC and FEV_3/FVC	Group 2 (n = 840) Only $FEV_3/FVC\downarrow$	Group 3 (n = 4,525) $FEV_1/FVC\downarrow$	*P* Value: Compare Group 1 to Group 2	*P* Value: Compare Group 2 to Group 3
BMI	31.5 ± 7.5	30.8 ± 7.0	28.6 ± 6.7	.005 (T)[a]	< .001 (T)[a]
Wt, kg	88.4 ± 22.3	87.5 ± 21.1	81.4 ± 21.0	.267 (T)	< .001 (T)[a]
Age, y	57.2 ± 14.5	61.2 ± 12.3	61.4 ± 13.4	< .001 (T)[a]	.617 (T)
FVC, % predicted	90.9 ± 15.8	91.0 ± 17.6	83.4 ± 19.5	.835 (T)	< .001 (T)[a]
FEV_1, % predicted	90.2 ± 16.1	82.6 ± 16.0	60.7 ± 20.0	< .001 (T)[a]	< .001 (T)[a]
FEV_1/FVC, %	77.4 ± 5.3	69.9 ± 3.7	55.3 ± 11.0	< .001 (T)[a]	< .001 (T)[a]
FEV_1/SVC, %	75.4 ± 6.3	68.1 ± 4.9	53.3 ± 11.6	< .001 (T)[a]	< .001 (T)[a]
FEV_3, % predicted	90.9 ± 15.9	84.5 ± 16.3	70.6 ± 20.2	< .001 (T)[a]	< .001 (T)[a]
FEV_3/FVC, %	91.0 ± 3.6	83.7 ± 2.9	75.8 ± 10.0	< .001 (W)[a]	< .001 (W)[a]
ExpT, s	9.7 ± 2.3	13.6 ± 3.1	13.7 ± 4.1	< .001 (W)[a]	.197 (W)
TLC, % predicted	97.1 ± 12.9	99.1 ± 13.2	108.2 ± 17.0	< .001 (T)[a]	< .001 (T)[a]
RV, % predicted	102.3 ± 26.9	109.4 ± 28.7	145.4 ± 48.4	< .001 (W)[a]	< .001 (W)[a]
RV/TLC, %	38.1 ± 9.5	40.5 ± 9.4	49.0 ± 11.8	< .001 (T)[a]	< .001 (T)[a]
RV/TLC, % predicted	105.4 ± 20.6	110.1 ± 22.1	133.0 ± 31.0	< .001 (T)[a]	< .001 (T)[a]
IC, % predicted	98.2 ± 21.7	94.5 ± 20.7	82.8 ± 24.6	< .001 (T)[a]	< .001 (T)[a]
DL, % predicted	80.7 ± 17.6	77.2 ± 17.9	67.3 ± 21.7	< .001 (T)[a]	< .001 (T)[a]
DL Hb Adj % predicted	81.9 ± 17.0	78.3 ± 17.4	68.1 ± 21.5	< .001 (T)[a]	< .001 (T)[a]
sGaw, L/s/cm H_2O/L	0.182 ± 0.087	0.151 ± 0.063	0.093 ± 0.053	< .001 (W)[a]	< .001 (W)[a]

Numeric data are given as mean ± SD. DL = diffusing capacity; ExpT = expiratory time; Hb Adj = hemoglobin adjusted; IC = inspiratory capacity; RV = residual volume; sGaw = specific conductance; SVC = slow vital capacity; (T) = two-sample *t* test; (W) = Wilcoxon rank sum test; Wt = weight. See Table 1 legend for expansion of other abbreviation.
[a]Statistically significant, $P < .017$.

Table 3—*Comparison Results for Degree of Obstruction Using All of the Patients (Including Reduced TLCs)*

Variable	Group 1 (n = 9,684) Normal FEV_1/FVC and FEV_3/FVC	Group 2 (n = 956) Only $FEV_3/FVC\downarrow$	Group 3 (n = 4,797) $FEV_1/FVC\downarrow$	*P* Value Compare Group 1 to Group 2	*P* Value Compare Group 2 to Group 3	*P* Value Compare Group 1 to Group 3
Smoker						
No	7,494 (77.4)	681 (71.2)	3,207 (66.9)	< .001(C)[a]	.008 (C)[a]	< .001 (C)[a]
Yes	2,190 (22.6)	275 (28.8)	1,590 (33.1)		…	…
Sex						
Female	5,701 (58.9)	455 (47.6)	2,403 (50.1)	< .001(C)[a]	.158 (C)	< .001 (C)[a]
Male	3,983 (41.1)	501 (52.4)	2,394 (49.9)		…	…
Race						
Black	3,818/9,285 (41.1)	372/933 (39.9)	1,716/4,690 (36.6)	.460 (C)	.058 (C)	< .001 (C)[a]
White	5,467/9,285 (58.9)	561/933 (60.1)	2,974/4,690 (63.4)		…	…
BMI	31.7 ± 7.6	31.0 ± 7.0	28.7 ± 6.8	.006 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
Wt, kg	89.2 ± 22.7	88.5 ± 21.3	81.9 ± 21.3	.352 (T)	< .001 (T)[a]	< .001 (T)[a]
Age, y	57.7 ± 14.6	61.2 ± 12.5	61.4 ± 13.5	< .001 (T)[a]	.718 (T)	< .001 (T)[a]
FVC, L	3.04 ± 1.01	3.13 ± 0.98	2.94 ± 1.03	.011 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FVC, % predicted	86.0 ± 18.5	87.5 ± 19.5	82.0 ± 20.0	.014 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1, L	2.37 ± 0.79	2.19 ± 0.69	1.66 ± 0.73	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1, % predicted	85.8 ± 18.3	79.5 ± 17.6	60.0 ± 19.9	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1/FVC, %	77.7 ± 5.5	69.9 ± 3.8	55.6 ± 10.9	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1/SVC, %	75.7 ± 6.4	68.1 ± 4.9	53.6 ± 11.5	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_3, L	2.78 ± 0.94	2.62 ± 0.84	2.26 ± 0.91	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_3, % predicted	86.2 ± 18.5	81.3 ± 18.1	69.6 ± 20.2	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_3/FVC, %	91.2 ± 3.6	83.7 ± 2.9	76.1 ± 9.9	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]
ExpT, s	9.6 ± 2.4	13.4 ± 3.1	13.5 ± 4.1	< .001 (W)[a]	.358 (W)	< .001 (W)[a]
TLC, L	5.02 ± 1.29	5.38 ± 1.28	5.97 ± 1.48	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
TLC, % predicted	91.8 ± 16.5	95.4 ± 16.1	105.9 ± 18.9	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
RV, L	1.90 ± 0.66	2.17 ± 0.68	2.92 ± 1.08	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]
RV, % predicted	96.8 ± 28.1	105.7 ± 29.3	142.0 ± 49.4	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]
RV/TLC, %	38.3 ± 9.6	40.6 ± 9.4	48.7 ± 11.8	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
RV/TLC, % predicted	105.6 ± 21.4	110.6 ± 22.8	132.4 ± 31.2	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
IC, L	2.24 ± 0.76	2.29 ± 0.74	2.05 ± 0.77	.056 (T)	< .001 (T)[a]	< .001 (T)[a]
IC, % predicted	92.4 ± 24.4	90.9 ± 22.3	81.4 ± 24.9	.068 (T)	< .001 (T)[a]	< .001 (T)[a]
DL, mL/mmHg/min	18.5 ± 6.3	18.1 ± 6.0	16.1 ± 6.7	.057 (T)	< .001 (T)[a]	< .001 (T)[a]
DL, % predicted	77.1 ± 19.3	75.0 ± 18.5	66.6 ± 21.7	.001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
DL Hb Adj	18.8 ± 6.1	18.4 ± 5.9	16.3 ± 6.6	.030 (T)	< .001 (T)[a]	< .001 (T)[a]
DLHbAdj, %	78.4 ± 18.7	76.1 ± 18.1	67.4 ± 21.5	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
sGaw, L/s/cm H_2O/L	0.186 ± 0.089	0.152 ± 0.064	0.094 ± 0.053	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]

Categorical data are given as fraction (%) of group; numeric data are given as mean ± SD. See Table 1 and 2 legends for expansion of abbreviations.

[a]Statistically significant, $P < .017$.

was below the 95% lower limit of normal (28.3% vs 33.5%, $P < .001$).

There did not appear to be racial differences (Table 1) when comparing the group with normal ratios to those with only a reduced FEV_3/FVC ($P = .664$), nor when the group with only a reduced FEV_3/FVC was compared with those with a reduced FEV_1/FVC ($P = .051$). When looking at all of the patients in Table 3, there is a racial difference comparing the group with normal ratios to those with a reduced FEV_1/FVC ($P < .001$), with the white population tending to show a greater percentage with obstruction based on a reduced FEV_1/FVC ratio.

The mean BMI progressively declined as obstruction worsened (Table 2). The group with normal ratios compared with the group with only a reduced FEV_3/FVC was 31.5 vs 30.8 ($P = .005$), with an even greater difference between the two obstructed groups (groups 2 and 3, 30.8 vs 28.6, $P < .001$). This suggests a greater burden of systemic disease in those with more advanced airways obstruction.

The mean age of the group with no obstruction on spirometry was significantly lower than the two obstructed groups (57.2 years, $P < .001$). But, there was no difference in the mean age between the two obstructed groups (61.2 years vs 61.4 years, $P = .617$).

The mean % predicted FVC was not significantly different between the group with no obstruction compared with those with only a reduced FEV_3/FVC (90.9% vs 91.0%, $P = .835$), but was significantly lower in the reduced FEV_1/FVC group (83.4%, $P < .001$). On the other hand, the mean % predicted IC was progressively and significantly lower comparing the three groups (98.2% vs 94.5% vs 82.8%, $P < .001$).

Table 4—*Comparison Results for Degree of Obstruction Without Restriction Based on TLC*

Variable	Group 1 (n = 7,937) Normal FEV_1/FVC and FEV_3/FVC	Group 2 (n = 840) Only $FEV_3/FVC\downarrow$	Group 3 (n = 4,525) $FEV_1/FVC\downarrow$	*P* Value Compare Group 1 to Group 2	*P* Value Compare Group 2 to Group 3	*P* Value Compare Group 1 to Group 3
Smoker						
No	6,102 (76.9)	602 (71.7)	3,011 (66.5)	< .001(C)[a]	.004 (C)[a]	< .001 (C)[a]
Yes	1,835 (23.1)	238 (28.3)	1,514 (33.5)			
Sex						
Female	4,730 (59.6)	403 (48.0)	2,276 (50.3)	< .001(C)[a]	.216 (C)	< .001 (C)[a]
Male	3,207 (40.4)	437 (52.0)	2,249 (49.7)			
Race						
Black	3,116/7,599 (41.0)	329/818 (40.2)	1,619/4,419 (36.6)	.664 (C)	.051 (C)	< .001 (C)[a]
White	4,483/7,599 (59.0)	489/818 (59.8)	2,800/4,419 (63.4)			
BMI	31.5 ± 7.5	30.8 ± 7.0	28.6 ± 6.7	.005 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
Wt, kg	88.4 ± 22.3	87.5 ± 21.1	81.4 ± 21.0	.267 (T)	< .001 (T)[a]	< .001 (T)[a]
Age, y	57.2 ± 14.5	61.2 ± 12.3	61.4 ± 13.4	< .001 (T)[a]	.617 (T)	< .001 (T)[a]
FVC, L	3.22 ± 0.98	3.25 ± 0.96	2.99 ± 1.03	.413 (T)	< .001 (T)[a]	< .001 (T)[a]
FVC, % predicted	90.9 ± 15.8	91.0 ± 17.6	83.4 ± 19.5	.835 (T)	< .001 (T)[a]	< .001 (T)[a]
FEV_1, L	2.49 ± 0.78	2.27 ± 0.68	1.68 ± 0.74	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1, % predicted	90.2 ± 16.1	82.6 ± 16.0	60.7 ± 20.0	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1/FVC, %	77.4 ± 5.3	69.9 ± 3.7	55.3 ± 11.0	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_1/SVC, %	75.4 ± 6.3	68.1 ± 4.9	53.3 ± 11.6	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_3, L	2.93 ± 0.92	2.72 ± 0.83	2.29 ± 0.92	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_3, % predicted	90.9 ± 15.9	84.5 ± 16.3	70.6 ± 20.2	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
FEV_3/FVC %	91.0 ± 3.6	83.7 ± 2.9	75.8 ± 10.0	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]
ExpT, s	9.7 ± 2.3	13.6 ± 3.1	13.7 ± 4.1	< .001 (W)[a]	.197 (W)	< .001 (W)[a]
TLC, L	5.29 ± 1.21	5.57 ± 1.21	6.09 ± 1.42	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
TLC, % predicted	97.1 ± 12.9	99.1 ± 13.2	108.2 ± 17.0	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
RV, L	2.00 ± 0.66	2.24 ± 0.68	2.99 ± 1.06	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]
RV, % predicted	102.3 ± 26.9	109.4 ± 28.7	145.4 ± 48.4	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]
RV/TLC, %	38.1 ± 9.5	40.5 ± 9.4	49.0 ± 11.8	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
RV/TLC, % predicted	105.4 ± 20.6	110.1 ± 22.1	133.0 ± 31.0	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
IC, L	2.38 ± 0.74	2.38 ± 0.73	2.09 ± 0.77	.909 (T)	< .001 (T)[a]	< .001 (T)[a]
IC, % predicted	98.2 ± 21.7	94.5 ± 20.7	82.8 ± 24.6	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
DL, mL/mmHg/min	19.4 ± 6.1	18.6 ± 6.0	16.3 ± 6.7	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
DL, % predicted	80.7 ± 17.6	77.2 ± 17.9	67.3 ± 21.7	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
DL Hb Adj	19.7 ± 6.0	18.8 ± 5.9	16.4 ± 6.7	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
DL Hb Adj, %	81.9 ± 17.0	78.3 ± 17.4	68.1 ± 21.5	< .001 (T)[a]	< .001 (T)[a]	< .001 (T)[a]
sGaw, L/s/cm H_2O/L	0.182 ± 0.087	0.151 ± 0.063	0.093 ± 0.053	< .001 (W)[a]	< .001 (W)[a]	< .001 (W)[a]

Categorical data are given as fraction (%) of group, numeric data are given as mean ± SD. See Table 1 and 2 legends for expansion of abbreviations.

[a]Statistically significant, $P < .017$.

This suggests progressively worsening air trapping between the groups. When including the patients with restriction on TLC (Table 3), the FVC was significantly lower in the normal ratios group compared with when only the FEV_3/FVC was reduced, but there was no difference in the IC. By including subjects with restrictive diseases, the lower FVC was expected as well as less air trapping reflected by the IC. Comparing the mean FEV_1 % predicted in the group with no obstruction to those with only a reduced FEV_3/FVC, and then the latter group to those with a reduced FEV_1/FVC, the FEV_1 progressively declined from 90.2% to 82.6% to 60.7%, with *P* values < .001.

Evidence of progressively increasing hyperinflation was noted in the TLC and RV, with increasing air trapping based on the RV/TLC ratio. Examining the progression in those with no obstruction on spirometry to those with only a reduced FEV_3/FVC, and then comparing this group to those with a reduced FEV_1/FVC, the mean TLC increased from 97.1% of predicted to 99.1% and 108.2%, respectively (*P* values between the three groups < .001). The mean RV percentage of predicted increased from 102.3% to 109.4% to 145.4% (*P* values between the three groups < .001). Air trapping progressively worsened between the three groups with the mean % predicted RV/TLC ratio increasing from 105.4% to 110.1% to 133.0% (*P* values between the groups < .001). If an isolated reduction in the FEV_3/FVC ratio is a finding of only mild airways disease, then one would expect to see only small but significant differences in the markers for mild hyperinflation and air trapping.

The mean DLCO corrected for hemoglobin showed a significant decline comparing the group with no

Table 5—*Comparing FEV_3/FVC to FEV_1/FVC*

Comparisons	All Patients (N = 15,437)	Excluding Patients with Restriction Based on TLC (n = 13,302)
Categories of obstruction		
Normal FEV_1/FVC + normal FEV_3/FVC	9,684	7,937
Normal FEV_1/FVC + reduced FEV_3/FVC	956	840
Reduced FEV_1/FVC + normal FEV_3/FVC	456	406
Reduced FEV_1/FVC + reduced FEV_3/FVC	4341	4,119
FEV_3/FVC compared with the FEV_1/FVC		
Sensitivity	0.905 (0.897-0.913)[a]	0.910 (0.902-0.919)[a]
Specificity	0.910 (0.905-0.916)[a]	0.904 (0.898-0.910)[a]
Postive predictive value	0 820 (0.809-0.830)[a]	0.833 (0.820-0.841)[a]
Negative predictive value	0.955 (0.951-0.959)[a]	0.951 (0.847-0.956)[a]

Assuming FEV_1/FVC is the gold standard for obstruction. See Table 1 legend for expansion of abbreviation.
[a]95% confidence limits.

obstruction, to when only the FEV_3/FVC ratio was reduced, and comparing the latter group to when the FEV_1/FVC was reduced (81.9% vs 78.3% vs 68.1%, $P < .001$). Whether the DLCO was corrected for hemoglobin or not gave similar results (Table 2).

Discussion

An FEV_1/FVC ratio below the 95% CI of predicted normal is the recommended standard of the ATS/ERS for identifying airways obstruction on spirometry. There has been confusion caused by conflicts with other recommendations such as the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines, which are based on observational evidence that an FEV_1/FVC ratio below 70% is indicative of COPD.[19,20] There has also been a plethora of literature using % predicted values based on opinions from observations rather than statistical analysis when interpreting other measurements, such as the FEF_{25-75}, in which the CIs are extremely wide with major overlap between normal and disease states.[4]

The FEV_3/FVC ratio is an often neglected and more sensitive tool for identifying early or mild airways disease than other commonly reported values.[2] This study demonstrates that patients with only a reduced FEV_3/FVC have significant physiologic differences compared with those with normal ratios consistent with the early development of air trapping (higher RV/TLC), hyperinflation (higher RV and TLC), and impairment of the gas exchanging surface (lower DLCO). The significance of these findings is further supported by these subjects having a lower mean FEV_1, and complements past research showing that a reduced value correlates with a smoking history.[2]

The total number of patients in which the reduced FEV_3/FVC was the only abnormality was not insignificant, consisting of 16% to 17% of the patients with airways obstruction. As a group, their mean lung volumes and DLCO were still within the normal range. This potentially could be useful information when evaluating smokers in whom otherwise we would report their spirometry as being normal. Because there was no age difference between the reduced FEV_3/FVC group compared with those with more severe obstruction, this may suggest they have a less progressive form of COPD or less advanced disease.

The FEV_1/FVC is considered the standard for identifying airway obstruction. Finding 456 subjects in the reduced FEV_1/FVC group that had a normal FEV_3/FVC (Table 5), we calculated the sensitivity and specificity of the FEV_3/FVC ratio for those with no restriction on TLC as well as all subjects (both > 90%). The positive predicted values were 82% and 83% with negative predicted values of > 95%. This analysis is valid if the FEV_3/FVC is measuring the same abnormality as the FEV_1/FVC. A more important question is whether the FEV_3/FVC is measuring a different, additional, or overlapping physiologic abnormality

Table 6—*If the FEV_1/FVC and FEV_3/FVC Are Both Measures Of Obstruction, Which Test Picks Up a Greater Proportion of the Obstructed Patients?*

If Either the FEV_3/FVC or FEV_1/FVC Is Reduced	All Patients (N = 5,753)	Patients With No Restriction on TLC (n = 5,365)
Normal FEV_1/FVC + reduced FEV_3/FVC	956	840
Reduced FEV_1/FVC + reduced FEV_3/FVC	4,341	4,119
Reduced FEV_1/FVC + normal FEV_3/FVC	456	406
Obstructed patients with reduced FEV_3/FVC, %	92.07%	92.43%
Obstructed patients with reduced FEV_1/FVC, %	83.38%	84.34%

See Table 1 legend for expansion of abbreviation.

than the FEV_1/FVC. Table 6 shows that the FEV_3/FVC identifies a greater percentage of obstructed patients than the FEV_1/FVC (92% vs 83%). These findings were similar whether looking at subjects with or without restriction on TLC.

There have been numerous studies trying to find more sensitive and specific ways to measure airflow obstruction, substituting one value for another (for example, substituting the FEV_3/FVC or FEV_1/FEV in 6 s for the FEV_1/FVC). Recent articles have suggested this may not be the correct approach because it assumes these ratios are measurements of the same thing. There may be reasons for one being normal while the other is abnormal. These studies suggest using these values in concordance with the FEV_1/FVC rather than as a substitute. For example, an isolated reduction of the FEV_1/FEV in 6 s can identify subjects with significant hyperinflation, air trapping, and diffusing impairment that is masked by having relatively shorter expiratory times (8 s) than what one sees in patients with COPD (15 s), and consideration should be given for more extensive testing.[21] This approach has also been suggested for the FEV_3/FVC ratio as well.[22]

Other factors may be involved in the discordance between these values, such as the effects of aging on these measurements and the performance of the test.

Conclusion

The FEV_3/FVC should be recommended as a routine measurement on spirometry in addition to the FEV_1/FVC ratio, and become a standard for identifying subjects with milder airways obstruction and lung injury when the FEV_1/FVC ratio is normal.

Acknowledgments

Author contributions: Dr Morris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Morris: contributed to the design of the study, defined the hypothesis, created the database, worked with the statistician, wrote and revised the manuscript.
Dr Coz: contributed to the design of the study, researched literature, worked with the statistician on the statistical analysis, and assisted in revising the manuscript.
Dr Starosta: contributed to the design of the study, researched literature, worked with the statistician on the statistical analysis, and assisted in writing and revising the manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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