FEV_1/FEV_6 to Diagnose Airflow Obstruction

Comparisons with Computed Tomography and Morbidity Indices

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Abstract

Rationale: FVC is a difficult maneuver for many patients, and forced expiratory volume in 6 seconds (FEV_6) has been proposed as a surrogate for FVC for the diagnosis of chronic obstructive pulmonary disease (COPD). Previous studies have performed head-to-head comparisons of these thresholds but did not examine their relationships with structural lung disease, symptoms, or exacerbations.

Objectives: To compare FEV_1/FEV_6 with FEV_1/FVC in the diagnosis of COPD-related morbidity and structural lung disease as assessed by CT.

Methods: We analyzed data from a large multicenter cohort study (COPDGene) that included current and former smokers (age 45–80 yr). Accuracy and concordance between the two ratios in diagnosing structural COPD was compared using CT measures of emphysema and airway disease and COPD-related morbidity to assess how the two ratios compare in defining disease.

Results: A total of 10,018 subjects were included. FEV_1/FEV_6 showed excellent accuracy in diagnosing airflow obstruction using $FEV_1/FVC < 0.70$ as a reference (area under curve, 0.99; 95% confidence interval [CI], 0.989–0.992; $P < 0.001$). $FEV_1/FEV_6 < 0.73$ had the best sum of sensitivity (92.1%; 95% CI, 90.8–92.4) and specificity (97.3%; 95% CI, 97.3–98.1). There was excellent agreement between the two diagnostic cutoffs ($\kappa = 0.90$; 95% CI, 0.80–0.91; $P < 0.001$). In comparison with control subjects and those positive by FEV_1/FVC alone, subjects positive by FEV_1/FEV_6 alone had greater gas trapping and airway wall thickness, worse functional capacity, and a greater number of exacerbations on follow-up. These relationships held true when disease definitions were made using the lower limits of normal.

Conclusions: FEV_1/FEV_6 can be substituted for FEV_1/FVC in diagnosing airflow obstruction and may better predict COPD-related pathology and morbidity.

Keywords: FEV_1/FEV_6; spirometry; COPD

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Chronic obstructive pulmonary disease (COPD) is defined by the presence of airflow obstruction identified by the ratio of the FEV_1 to the FVC below a certain threshold (1). Measurement of FVC can be uncomfortable for patients. It is hard to reproduce, entails using spirometers capable of detecting very low flow rates, and requires trained personnel for quality control (2, 3). Because the majority of exhalation is complete within about 6 seconds in most subjects (4), the forced expiratory volume in 6 seconds (FEV_6) has been proposed as a surrogate for FVC and has a number of potential advantages,

including being easier to perform (using less sophisticated and inexpensive handheld spirometers) and having a distinct and perhaps more reproducible test endpoint (5–9). Some subjects with significant air trapping can take as long as 20 seconds or more for a complete FVC maneuver (6), which has raised concerns that the use of FEV_1/FEV_6 may lead to overestimation of the FEV_1/FVC ratio and thus miss a diagnosis of COPD. Previous studies showing that FEV_6 can likely be substituted for FVC considered FEV_1/FVC as the gold standard for disease (5–8). When one ratio is used as gold standard, the other ratio will indicate that some subjects are misclassified (10), and in the absence of a true gold standard for disease, the implications of these misclassifications are not clear. In this regard, computed tomographic (CT) images have been shown to correlate well with pathology and with clinical symptoms (11), and quality-of-life questionnaires specific for respiratory disease can further discern the presence of morbidity (12).

We hypothesized that FEV_6 can be substituted for FVC in the diagnosis of airflow obstruction. We compared the utility of the two spirometric ratios in identifying CT-measured emphysema and airway disease as well as COPD-related symptoms, quality of life, functional capacity, and exacerbation risk.

Methods

Study Population and Physiologic Assessments

Subjects from a large multicenter cohort study (COPDGene) that included smokers and former smokers 45 to 80 years of age were included in the study. The study enrolled 10,364 subjects. Details of the study protocol have been previously published (13, 14). Sixty-four subjects with extensive bronchiectasis or interstitial lung disease identified on CT were excluded from this study. Airflow obstruction was assessed by performing pre- and postbronchodilator spirometry using the ndd Easy-One spirometer in conformance with the American Thoracic Society criteria (2) (details on spirometric testing are provided in the online supplement). Postbronchodilator values were used, and the best values for each subject for FEV_1, FEV_6, and FVC were chosen. Two hundred eighty-two subjects were not able to exhale to 6 seconds and were excluded from analyses. St George's Respiratory Questionnaire (SGRQ) scores were used to assess respiratory disease–related health impairment and quality of life (15). All subjects performed a 6-minute walk test according to the American Thoracic Society guidelines to assess functional capacity (13). Dyspnea was measured using the Modified Medical Research Council (MMRC) dyspnea score (16). Using the above-mentioned parameters and the body mass index (BMI), the BODE (The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) index was calculated to predict COPD-related mortality (17). The COPDGene study was approved by the institutional review boards of all 21 participating centers, and each subject gave written informed consent before participation in the study.

Imaging

Volumetric CT scans were obtained at maximal inspiration (TLC) and end-tidal expiration (FRC). Emphysema and gas trapping were quantitated using 3D Slicer software (www.airwayinspector.org), and airway dimensions were measured using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, IA) (13). Emphysema was quantified by using the percentage of lung volume at TLC with attenuation less than −950 Hounsfield Units (HU) (low attenuation area, % $LAA950_{insp}$) and percentage of voxels below the 15th percentile (Perc15) (13, 18). We quantified gas trapping as the percentage of lung volume at FRC with attenuation less than −856 HU ($\%LAA856_{exp}$) (19). We used Wall area percentage of segmental airways (Wallarea%) to quantify airway disease (13). Acceptable measures of emphysema, gas trapping, and Wall area percentage were available in 9,358, 8,467, and 9,376 subjects, respectively.

Case Definitions

The presence of COPD was spirometrically defined by $FEV_1/FVC < 0.70$ per the Global Initiative for Chronic Obstructive Lung Disease (GOLD COPD) guidelines (1). Because FEV_6 is usually lower than FVC, receiver operating characteristics were used to define the best value for FEV_1/FEV_6 that had the highest sum of sensitivity and specificity in diagnosing airflow obstruction as defined by $FEV_1/FVC < 0.70$. Subjects with FEV_1/FEV_6 below this threshold of 0.73 were categorized as having airflow obstruction by FEV_6 criteria. Subjects who were positive by both FEV_1/FVC and FEV_1/FEV_6 criteria were defined as having COPD, and subjects who were negative by both criteria were deemed to have no airflow obstruction. Discordant subjects with $FEV_1/FVC < 0.70$ but $FEV_1/FEV_6 > 0.73$ were termed FVC-COPD; those with $FEV_1/FEV_6 < 0.73$ but $FEV_1/FVC > 0.70$ were termed FEV_6-COPD. Because there is controversy about the usage of fixed thresholds to define COPD irrespective of age, we performed separate analyses after categorizing subjects with FEV_1/FVC less than the 5th percentile of expected value for age, race, and sex as having FVC-COPD–lower limit of normal (LLN) (20). Reference values were drawn from the National Health and Nutrition Examination Survey (NHANES) III cohort (20). Subjects who had FEV_1/FEV_6 less than the 5th percentile for age, race, and sex were categorized as having FEV_6-COPD-LLN (21). We used $\geq$ 5% $LAA950_{insp}$ to define emphysema and $\geq$ 15% $LAA856_{exp}$ to define gas trapping on quantitative CT scans (22).

Follow-Up

Subjects were contacted every 6 months by an automated telephony system using a validated questionnaire (23). Exacerbations were defined as episodes requiring use of antibiotics or systemic steroids for acute worsening of respiratory symptoms. Severe exacerbations were defined as those requiring hospitalization.

Statistical Analyses

All values are expressed as mean (±SD). Receiver operating characteristic analyses were performed to measure the accuracy of FEV_1/FEV_6 in comparison with FEV_1/FVC and to identify the FEV_1/FEV_6 cutoff that had the best sum of sensitivity and specificity for diagnosing airflow obstruction defined by $FEV_1/FVC < 0.70$. Concordance between COPD by FEV_1/FVC and FEV_1/FEV_6 thresholds was assessed using κ statistics. Two-by-two tables were drawn for the presence of disease by FEV_1/FVC using FEV_1/FEV_6 as a diagnostic test to assess sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. Similarly, 2×2 tables were constructed for emphysema and gas

trapping to compare accuracy of FEV_1/FEV_6 and FEV_1/FVC cutoffs in identifying these abnormalities. Baseline characteristics of subjects concordant and discordant for airflow obstruction were compared with smokers concordant for not having airflow obstruction using ANOVA. We used the Tukey test for *post hoc* pairwise multiple comparisons between groups. We categorized CT and functional variables (except MMRC) by quartiles and performed cumulative logistic regression models to predict higher quartiles. Because MMRC has a narrow range, we did not categorize it by quartiles to perform the logistic model. With "normal" control subjects as the reference group, odds ratios (ORs) and 95% confidence intervals (CIs) for CT and functional variables in each COPD group were estimated, adjusted for age, race, sex, height, and BMI. Similar analyses were repeated to compare FEV_6-COPD and FVC-COPD. Intraclass correlation coefficients with two-way mixed model and absolute agreement definition for interrater analysis were used to assess repeatability of each spirometric measurement. Bland-Altman plots were generated to evaluate variations in accuracy over the range of airflow obstruction by GOLD stages. Cox proportional hazards were calculated for exacerbations on follow-up. A P value < 0.05 was deemed statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS 20.0; SPSS Inc., Chicago, IL) and SAS version 9.2 (SAS Institute, Inc.).

Results

A total of 10,018 subjects were included (mean age, 59.7 ± 9 yr). This included predominantly current and former smokers and 108 healthy nonsmokers. Male subjects constituted 53.4% of the cohort; 67.7% were Caucasian, and 32.3% were African American. The prevalence of airflow obstruction using the GOLD criteria was 44.7%. Of these, 747 had GOLD grade I (16.7%), 1,920 had GOLD grade II (42.9%), 1,162 had GOLD grade III (25.9%), and 604 (13.5%) had GOLD grade IV airflow obstruction. The prevalence of airflow obstruction using LLN for FEV_1/FVC was 38.4%.

FEV_1/FEV_6 showed excellent accuracy in diagnosing airflow obstruction using $FEV_1/FVC < 0.70$ as reference (area under curve, 0.99; 95% CI, 0.989–0.992; $P < 0.001$) (Figure 1). Sensitivity and specificity at different FEV_1/FEV_6 cutoffs are shown in Table 1. $FEV_1/FEV_6 < 0.73$ had the best sum of sensitivity (92.1%; 95% CI, 90.8–92.4) and specificity (97.3%; 95% CI, 97.3–98.1). There was excellent agreement between the two diagnostic cutoffs (κ = 0.90; 95% CI, 0.80–0.91; $P < 0.001$).

A 2×2 table also showed that, in comparison to $FEV_1/FVC < 0.70$, $FEV_1/FEV_6 < 0.73$ had excellent positive predictive value (PPV) (97%; 95% CI, 96.4–97.5) and negative predictive value (NPV) (93.5%; 95% CI, 92.9–94.1). The positive likelihood ratio was 39.6 (95% CI, 33.4–47.1), and the negative likelihood ratio was 0.09 (95% CI, 0.08–0.09). We found similar results using the LLN for FEV_1/FVC and FEV_1/FEV_6 (*see* Table E1 in the online supplement).

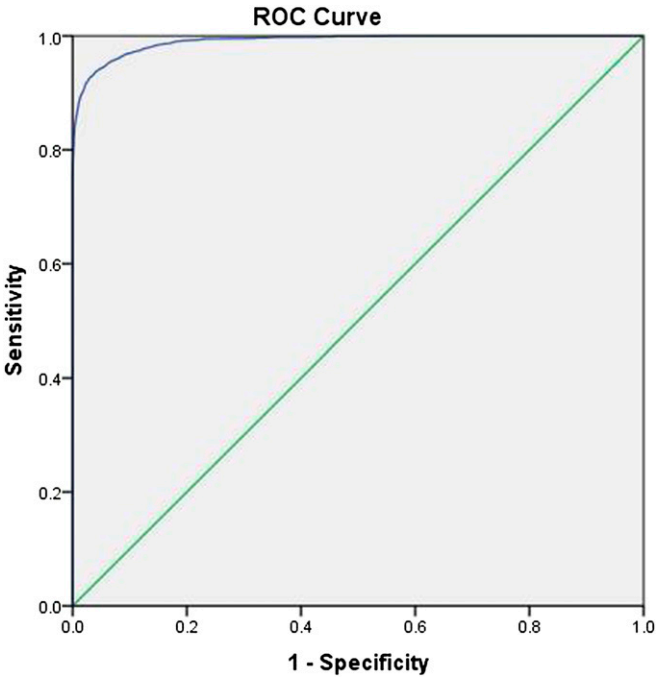

Figure 1. Receiver operating characteristic (ROC) curve comparing sensitivity and specificity of FEV_1/FEV_6 against $FEV_1/FVC < 0.70$.

Comparison of demographics, CT measures of emphysema, gas trapping, and airway wall thickness, as well as measures of respiratory morbidity (MMRC, 6-min walk distance, and SGRQ scores) and BODE score, a composite index of COPD-related mortality, is shown in Table 2. Univariate comparisons between FEV_6-COPD and FVC-COPD are also shown in Table 2. Fewer subjects were positive by FEV_1/FEV_6 only (1.3%) in comparison to those positive by FEV_1/FVC only (3.7%). Although the higher number of discordant positives for FEV_1/FVC could have been influenced by the threshold chosen for FEV_1/FEV_6, we did find that FEV_6-COPD had more morbidity than FVC-COPD. Subjects with FEV_6-COPD had more impairment in

Table 1. Sensitivity and specificity at various FEV_1/FEV_6 cut-offs in comparison with $FEV_1/FVC < 0.70$

FEV_1/FEV_6	0.70	0.71	0.72	0.73*	0.74	0.75
Sensitivity	78.3	83.2	87.8	92.1	95.1	97.4
Specificity	99.1	99.7	99	97.3	93.9	88.7

Definition of abbreviation: FEV_6 = forced expiratory volume in 6 s.
*Highest sum of sensitivity and specificity.

quality-of-life indices and had a shorter 6-minute walk distance than normal control subjects and subjects with FVC-COPD. Subjects with FEV_6-COPD also had greater airway disease, as evidenced by greater gas trapping and wall thickness (Table 2).

After adjustment for age, sex, race, height, and BMI, subjects with FEV_6-COPD were more likely to be in a higher quartile of gas trapping (adjusted OR, 1.78; 95% CI, 1.19–2.66; $P = 0.005$), a higher quartile of airway wall thickness (adjusted OR, 2.44; 95% CI, 1.67–3.57; $P < 0.001$), and a lower quartile of 6-minute walk distance than subjects with FVC-COPD (adjusted OR, 0.44; 95% CI, 0.30–0.63). Compared with control subjects, subjects with FEV_6-COPD were also more likely to be in a higher quartile of emphysema, gas trapping, airway wall thickness, MMRC, and SGRQ and in a lower quartile of 6-minute walk distance than control subjects (Tables 3 and 4 and Tables E2 and E3).

For detecting emphysema at 5% LAAinsp<-950HU (prevalence, 30.7%), $FEV_1/FEV_6 < 0.73$ and $FEV_1/FVC < 0.70$ had similar numerical sensitivity (80.8; 95% CI, 79.3–82.2 vs. 82.9; 95% CI, 81.4–84.2), specificity (74.8; 95% CI, 73.8–75.9 vs. 72; 95% CI, 70.9–73.1), PPV (58.7; 95% CI, 57.2–60.3 vs. 56.7; 95% CI, 55.2–58.2) and NPV (89.8; 95% CI, 89–90.6 vs. 90.5; 95% CI, 89.6–91.3). The positive and negative likelihood ratios were 3.21 (95% CI, 3.07–3.36) versus 2.96 (95% CI, 2.84–3.09) and 0.26 (95% CI, 0.24–0.28) versus 0.24 (95% CI, 0.22–0.26), respectively. For detecting gas trapping at 15% LAAexp<-856HU (prevalence, 49.7%), $FEV_1/FEV_6 < 0.73$ and $FEV_1/FVC < 0.70$ had similar numerical sensitivity (70.6; 95% CI, 69.2–71.9 vs. 72.8; 95% CI, 71.5–74.2), specificity (85.9; 95% CI, 84.8–86.9 vs. 82.8; 95% CI, 81.6–83.9), PPV (83.2; 95% CI, 81.9–84.4 vs. 80.7; 95% CI, 79.4–81.9), and NPV (74.7; 95% CI, 73.5–75.9 vs. 75.5; 95% CI, 74.3–76.8). The positive and negative likelihood ratios were 5.0 (95% CI, 4.63–5.4) versus 4.23 (95% CI, 3.95–4.53) and 0.34 (95% CI, 0.33–0.36) versus 0.33 (95% CI, 0.31–0.35), respectively.

We had follow-up data for 8,096 subjects for 2.4 ± 1.4 years (range, 9 d to 4.8 yr). Compared with control subjects, the unadjusted hazard ratios for exacerbations in COPD, FVC-COPD, and FEV_6-COPD were 2.15 (95% CI, 1.96–2.36; $P < 0.001$), 0.89 (95% CI, 0.68–1.18; $P = 0.42$), and 1.68 (95% CI, 1.14–2.47; $P = 0.008$), respectively, and those for severe exacerbations were 2.99 (95% CI, 2.58–3.48; $P < 0.001$), 0.66 (95% CI, 0.38–1.12; $P = 0.12$), and 2.45 (95% CI, 1.43–4.20; $P = 0.001$), respectively.

Repeatability was excellent for all three spirometric measurements. The intraclass correlation coefficients for FEV_1, FVC, and FEV_6 were 0.993 (95% CI, 0.986–0.995; $P < 0.001$), 0.989 (95% CI, 0.979–0.994; $P < 0.001$), and 0.991 (95% CI, 0.984–0.994; $P < 0.001$), respectively. The major cause of discordance between FVC and FEV_6 is

Table 2. Comparison of demographics, imaging, and quality of life indices between concordant and discordant groups

Demographics	"Normal" Control Subjects (FEV_1/FVC and FEV_1/FEV_6 negative) (*n = 5,410*)	COPD (FEV_1/FVC and FEV_1/FEV_6 positive) (*n = 4,105*)	FVC-COPD (FEV_1/FVC positive and FEV_1/FEV_6 negative) (*n = 375*)	FEV_6-COPD (FEV_1/FEV_6 positive and FEV_1/FVC positive) (*n = 128*)
Age, yr	56.9 (8.4)	63.2 (9)*	61.4 (8.1)*	58.3 (9)†
Sex, % male	51.2	56	56	57
Race, % Caucasian	59.9	77.5	75.7	60.9
BMI, kg/m^2	29.5 (6.2)	27.8 (6.1)*	29.2 (6.1)	28.4 (6.8)
Pack-years	38.3 (21)	52.3 (27.4)*	44 (23.3)*	44.1 (30.4)*
Spirometry				
FEV_1, L	2.73 (0.73)	1.58 (0.75)*	2.51 (0.64)*	2.32 (0.76)*
FEV_1, %Pred	92.1 (15.5)	54.9 (21.8)*	84.7 (13.8)*	77.3 (16.8)*†
FVC, L	3.5 (0.93)	3.04 (1.03)*	3.73 (0.95)*	3.29 (1.07) †
FEV_6, L	3.39 (0.89)	2.64 (0.96)*	3.36 (0.85)	3.23 (1.05)
FEV_1/FVC	0.78 (0.05)	0.51 (0.13)*	0.67 (0.02)*	0.71 (0.01)*†
FEV_1/FEV_6	0.81 (0.04)	0.58 (0.11)*	0.75 (0.01)*	0.72 (0.01)*†
CT				
TLC, L	5.16 (1.28)	6.03 (1.45)*	5.62 (1.33)*	5.41 (1.42)
FRC, L	2.71 (0.72)	3.96 (1.22)*	3 (0.76)*	3.21 (0.93)*
%LAA<-950insp	1.9 (2.5)	12.4 (12.4)*	3.3 (3.6)*	2.6 (3.3)
Perc15	−903.6 (25.8)	−937.6 (28)*	−914.2 (22.8)*	−909.3 (25.4)
%LAA<-856exp	10.7 (9.4)	37.8 (20.5)*	15.3 (9.9)*	18.8 (13.2)*
Wallarea%	60.5 (3.1)	62.6 (3.2)*	60.4 (2.8)	62.2 (3.4)*†
QoL				
MMRC	0.9 (1.3)	2 (1.5)*	1 (1.3)	1.3 (0.7)*
6MWD, ft	1,456 (365)	1211 (400)*	1480 (356)	1293 (383)*†
BODE	0.6 (1)	2.7 (2.1)*	0.6 (1)	1.2 (1.5)*†
SGRQ	19.2 (19.6)	38.4 (22.7)*	20.9 (19.2)	26.6 (23.1)*†

Definition of abbreviations: BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity index; COPD = chronic obstructive pulmonary disease; FEV_6 = forced expiratory volume in 6 s; %LAA<-856exp = %low attenuation area below a threshold of −856 Hounsfield Units at end expiration; %LAA<-950insp = %low attenuation area below a threshold of −950 Hounsfield Units at end inspiration; MMRC = Modified Medical Research Council dyspnea scale; 6MWD = 6-minute-walk distance; Perc15 = density of lung in Hounsfield Units below which 15% of the voxels had the lowest attenuation numbers at full inspiration; SGRQ = St. George's Respiratory Questionnaire; Wallarea% = bronchial wall area at segmental level.

*$P < 0.05$ compared with "normal" control subjects.

†$P < 0.05$ for FEV_6-COPD compared with FVC-COPD.

Table 3. Odds ratios of chronic obstructive pulmonary disease diagnostic criteria for predicting imaging measures of chronic obstructive pulmonary disease*

Parameter†	$\%LAA_{insp}<-950HU$			$\%LAA_{exp}<-856HU$			Wallarea%		
	OR‡	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
COPD	8.49	7.74–9.32	<0.001	16.69	14.99–18.59	<0.001	5.39	4.93–5.89	<0.001
FEV_6-COPD	1.43	1.02–1.99	0.04	3.37	2.37–4.81	<0.001	3.01	2.15–4.21	<0.001
FVC-COPD	1.69	1.40–2.06	<0.001	1.90	1.54–2.33	<0.001	1.23	1.01–1.50	0.04
FEV_6-COPD§	0.31	−1.33–1.94	0.38	1.78	1.19–2.66	0.005	2.44	1.67–3.57	<0.001

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_6 = forced expiratory volume in 6 s; OR = odds ratio; %LAA<−856exp = %low attenuation area below a threshold of −856 Hounsfield Units at end expiration; %LAA<−950insp = %low attenuation area below a threshold of −950 Hounsfield Units at end inspiration; Wallarea% = bronchial wall area at segmental level.
*Model adjusted by race, sex, age, height, and body mass index. All comparisons made for each group in reference with normal control subjects.
†COPD includes subjects positive by both criteria ($FEV_1/FVC < 0.70$ and $FEV_1/FEV_6 < 0.73$). FEV_6-COPD includes subjects positive by $FEV_1/FEV_6 < 0.73$ only. FVC-COPD includes subjects positive by $FEV_1/FVC < 0.70$ only.
‡Odds ratio indicates odds of being in more severe quartile for each variable.
§Comparisons made with FVC-COPD as the reference group.
Quartile thresholds include %LAAinsp<−950HU: 0 to < 0.62, 0.62 to < 2.06, 2.06 to < 6.86, and ⩾ 6.86% percent; %LAAexp<−856HU: 0 to < 6.61, 6.61 to < 14.80, 14.80 to < 32.32, and ⩾ 32.32%; and Wallarea%: 0 to 59, 59 to < 61, 61 to < 64, and ⩾ 64%.

prolonged expiration time (forced expiratory time [FET]) in some individuals. FET ranged from 1.5 to 40.4 seconds (mean, 10.5 ± 3.9 s). There were significant differences in FET between all four groups (9 ± 2.5 s in control subjects, 12.2 ± 4.4 in COPD, 7.3 ± 1.1 in FEV_6-COPD, and 14.4 ± 3.7 in FVC-COPD; $P < 0.001$ for all comparisons). The difference between FVC and FEV_6 was 111.2 (96.9) ml in control subjects, 392.6 (296) ml in subjects with COPD by both criteria, 61.5 (47.8) ml in FEV_6-COPD, and 374.7 (163.9) ml in FVC-COPD. Bland Altman analyses revealed that the difference between FEV_6 and FVC increased with greater GOLD stage, ranging from 0.11 ± 0.10 L in normal control subjects to 0.53 ± 0.35 L in GOLD Stage IV (*see* Table E4 and Figure E1 for more details). However, both discordant groups had FEV_1/FVC very close to their predicted LLN (−0.03 ± 0.02 for FEV_6-COPD and –0.001 ± 0.03 for FVC-COPD), suggesting that the divergence in measurement with increasing disease severity does not affect diagnosis once the specified threshold is reached.

Discussion

We have shown that $FEV_1/FEV_6 < 0.73$ could substitute for $FEV_1/FVC < 0.70$ to diagnose airflow obstruction and that an $FEV_1/FEV_6 < 0.73$ is significantly associated with CT measures of emphysema, COPD quality-of-life and functional indices, and subsequent exacerbations even with $FEV_1/FVC \geqslant 0.70$. This substitution holds true even when LLN is used. Using CT measures of emphysema, quality-of-life and functional indices, and exacerbation rate on follow-up, we have shown that FEV_1/FEV_6 is superior to FEV_1/FVC for the diagnosis of COPD-related morbidity.

Previous studies have shown that FEV_1/FEV_6 can be substituted for FEV_1/FVC in the diagnosis of airflow obstruction and restriction (6, 7, 24) and that the FEV_6 maneuver is more reproducible than FVC (6), but these studies were limited by using prebronchodilator values, by not using races other than Caucasian, and by

Table 4. Odds ratios of chronic obstructive pulmonary disease diagnostic criteria for predicting quality of life indices of chronic obstructive pulmonary disease*

Parameter†	MMRC			Total SGRQ			6-Min-Walk Distance		
	OR‡	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	P Value
COPD	5.58	5.12–6.08	<0.001	7.07	6.49–7.73	<0.001	0.27	0.25–0.29	<0.001
FEV_6-COPD	1.83	1.32–2.54	<0.001	1.96	1.43–2.69	<0.001	0.42	0.30–0.58	<0.001
FVC-COPD	1.34	1.10–1.65	0.005	1.53	1.26–1.85	<0.001	0.95	0.78–1.16	0.61
FEV_6-COPD§	1.36	0.93–1.99	0.11	1.28	0.89–1.84	0.18	0.44	0.30–0.63	<0.001

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_6 = forced expiratory volume in 6 s; MMRC = Modified Medical Research Council dyspnea scale; OR = odds ratio; SGRQ = St. George's Respiratory Questionnaire.
*Model adjusted by race, sex, age, height, and body mass index. All comparisons made for each group in reference with normal control subjects.
†COPD includes subjects positive by both criteria, $FEV_1/FVC < 0.70$ and $FEV_1/FEV_6 < 0.73$. FEV_6-COPD includes subjects positive by $FEV_1/FEV_6<0.73$ only. FVC-COPD includes subjects positive by $FEV_1/FVC < 0.70$ only.
‡Odds ratio indicates odds of being in more severe quartile for each variable.
§Comparisons made with FVC-COPD as the reference group.
Quartile thresholds include SGRQ: 0 to < 7, 7 to < 22, 22 to < 44, and > 44 and 6-min-walk distance: 0 to < 1115, 1,115 to < 1383, 1,383 to < 1623, and > 1623 ft.

excluding a large proportion of tests because they lasted less than 6 seconds. Further validating the utility of FEV_1/FEV_6, Enright and colleagues used follow-up data from 2,827 subjects participating in the Lung Health Study and showed that airflow obstruction as defined by FEV_1/FEV_6 could be used as a substitute for FEV_1/FVC in predicting lung function decline with time (5). FEV_1/FEV_6 also predicts all-cause mortality and FEV_1/FVC in elderly subjects (25). None of these studies compared the relationship between each spirometric measure and other assessments of disease because the researchers assumed that FEV_1/FVC was the reference standard for diagnosis of airflow obstruction. In contrast, Morris and colleagues, in a large, retrospective study of prebronchodilator spirometric tests, found that subjects who were positive by FEV_1/FEV_6 criteria alone had more hyperinflation and air trapping and lower inspiratory capacity and diffusion capacity of carbon monoxide than subjects with reduced FEV_1/FVC alone (26).

FVC is a harder maneuver to reproduce than FEV_6, especially in subjects with greater air trapping, the very population in which some researchers have criticized the FEV_1/FEV_6 ratio for underestimating the volume and hence creating a higher ratio (3). Subjects with significant air trapping might reach and exceed their equal pressure point earlier and more peripherally before complete emptying and hence have FVC lower than expected for age, creating a falsely high FEV_1/FVC, a phenomenon that should be less likely to occur if FEV_6 is used. For some subjects with very severe air trapping, the equal pressure point may fall just outside the 6-second time mark but well within their actual FVC if a full expiratory maneuver were possible. In this group, FEV_6 might be proportionately reduced but not to the point of complete cessation of airflow and hence not to the end point for testing. Our results indicate that those who were able to exhale to a longer FET were more likely to be in the FVC-COPD group.

A study by Hansen and colleagues raised questions about the accuracy of substituting FEV_1/FEV_6 for FEV_1/FVC in a large cohort of subjects using the original NHANES III cohort because they found greater false negatives using LLN of FEV_1/FVC as gold standard, unlike other large studies that found higher false positives (10). However, these analyses were performed in the original derivative cohort for reference values for LLN, and using FEV_1/FVC as gold standard would by definition make FEV_1/FEV_6 seem a lesser measure. Similar comparisons were made in other studies that used a fixed ratio but did not change the FEV_1/FEV_6 cutoff to a higher value (27). The cutoff of 0.73 we found in our study has been found by other researchers (8, 24) and has been reproduced in elderly populations (8). Some other studies have reported lower specificity for FEV_1/FEV_6 (28, 29), likely illustrating the inherent problems with reference equations applied to populations they were not derived from, and also from using FEV_1/FVC as gold standard without any other measure to corroborate the presence of disease (10, 28, 29).

We add to the literature by demonstrating that FEV_1/FEV_6 predicts COPD-related structural disease on CT and on COPD-related morbidity better than FEV_1/FVC. In patients with severe disease, the spirometric ratio chosen for diagnosis likely does not matter because these patients have ratios well below the chosen cut offs, and there is a high degree of concordance. The selection of spirometric ratio is especially pertinent in milder cases in whom symptoms, quality of life, and exacerbation risk are highly variable, and we have shown that, in discordant cases, FEV_1/FEV_6 performs better than FEV_1/FVC in predicting these outcomes.

Our study has some limitations. Not all subjects could perform an expiratory maneuver that lasted 6 seconds, and these subjects had to be excluded. However, due to strict quality control, this number was very low (2.7%) and was much lower than the third of patients excluded in some other studies (6, 7, 25, 28). It has been proposed that the highest FVC in the first 6 seconds be used in these cases because this would be equal to the FVC and hence increase the agreement between FEV_1/FVC and the 6-second volume ratios (21). Indeed, the reference equations for FEV_6 used the maximum attainable volume in 6 seconds (21). Although other studies support the use of FEV_1/FEV_6 in diagnosing restrictive lung disease (6, 7, 24, 30), we did not analyze this because spirometry alone is not accurate in diagnosing restriction (31). The likelihood ratios for predicting CT emphysema and airway wall thickness for both spirometric thresholds fell short of conventionally accepted significance thresholds, likely reflecting the relative insensitivity of spirometry in diagnosing CT-detected emphysema (32). We used a fixed cutoff for FEV_1/FEV_6 of < 0.73, but different cutoffs may be useful depending on the desired sensitivity and specificity. Lastly, the study enrolled subjects who were current or former smokers; therefore, the results might not be applicable to populations at low risk for COPD.

Our study confirms prior observations that the FEV_6 maneuver is a reliable alternative to FVC for the diagnosis of intrathoracic airflow obstruction, and we now establish that FEV_1/FEV_6 is superior to FEV_1/FVC in detecting respiratory symptoms and CT abnormalities associated with COPD. These findings support substituting FEV_1/FEV_6 for FEV_1/FVC in diagnosing airflow obstruction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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