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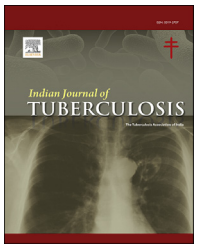

Original Article

FEV1/FEV6 is effective as a surrogate for FEV1/FVC in the diagnosis of chronic obstructive pulmonary disease

Palanisamy Venkatachalam, Dharm Prakash Dwivedi[*], *Vishnukanth Govindraj*

Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India

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ABSTRACT

Background and objective: Chronic Obstructive Pulmonary Disease (COPD) causes substantial morbidity and mortality across the globe. Diagnosis of COPD requires post-bronchodilator FEV1/FVC <0.70 as per GOLD Guidelines. FVC maneuver requires a minimum of 6 seconds of forceful expiration with no flow for 1 second for an accepted effort, which lacks any fixed cut-off point. This leads to discomfort, especially in advanced COPD and old aged population. We conducted this study to find the utility of FEV1/FEV6 as a surrogate for FEV1/FVC, the correlation between the two ratios, and the fixed cut-off value of FEV1/FEV6 for COPD diagnosis.

Methods: This was a prospective, cross-sectional study approved by the institutional ethics committee conducted from January 2017 to November 2018. Consented patients above 18 years suspected of COPD underwent Spirometry as per ATS guidelines. FEV1, FEV6, FEV1/FEV6 and FEV1/FVC ratios were recorded from the best acceptable maneuver.

Results: Out of 560 screened patients, 122 diagnosed as COPD. The correlation coefficient between the post-bronchodilator FEV1/FVC ratio and FEV1/FEV6 ratio was 0.972 ($p < 0.01$). The relationship between the post-bronchodilator FEV1/FVC ratio and FEV1/FEV6 ratio (linear regression analysis) was found out as: FEV1/FVC = −1.845 + 1.009(FEV1/FEV6). Using this formula, the post-bronchodilator FEV1/FEV6 value of 71.845 was obtained corresponding to the post-bronchodilator FEV1/FVC value of 70.00.

Conclusion: We found a positive correlation coefficient ($r = 0.972$, $p < 0.001$) between the FEV1/FEV6 and FEV1/FVC ratios and the cut off value of 71.845 ($p < 0.01$) for the post-bronchodilator FEV1/FEV6 ratio for the diagnosis of COPD. Thus FEV1/FEV6 should be used as a surrogate for FEV1/FVC for the diagnosis of COPD.

* *Corresponding author*. Department of Pulmonary Medicine, JIPMER, Dhanvantari Nagar, Pondicherry, 605006, India.
E-mail address: dippyd@gmail.com (D.P. Dwivedi).
dpdwivedi

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1. Introduction

1.1. Background

Chronic Obstructive Pulmonary Disease (COPD) causes substantial mortality and morbidity worldwide. The estimated global prevalence of COPD was approximately 384 million (11.7%) in 2010.[1] An increasing number of smokers in developing nations and a rise in the number of the elderly population in developed economies is contributing to the increase in the incidence of COPD. Estimated deaths of 4.5 million are projected from COPD by 2030.[2,3] Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 criteria requires post-bronchodilator forced expiratory volume1/forced vital capacity (FEV1/FVC) < 0.70 to confirm the presence of persistent airflow limitation and hence the diagnosis of COPD.[4] FVC maneuver requires a patient to blow for at least 6 seconds (3 seconds for kids below 12 years) and it is accepted when there is no flow for 1 second or more. As COPD patients have dynamic compression of airways, they require more time to exhale (sometimes 12–20 seconds), which may cause exhaustion, dizziness, and syncope due to reduced venous return to heart.[5] There is no fixed cut-off for the duration of exhalation. FEV1/FVC fixed ratio of 0.7 also tends to overdiagnose COPD, especially in the elderly population. Various authors have proposed a lower limit of normal (LLN) as the cut-off criteria for the diagnosis of obstructive airway disease.[5–7] FEV6 (the volume of air forcefully exhaled in 6 seconds) has also been proposed as a replacement or surrogate for FVC in spirometry.[7–9] FEV6 maneuver has a distinct endpoint of six seconds and is less physically demanding than FVC. FEV6 is more reproducible and reliable than FVC for the diagnosis of COPD.[5] FEV6 can also be measured using portable handheld spirometers, which are inexpensive and easy to use.[8,9] This makes it suitable for mass screening and bedside use. Several studies have investigated the utility of FEV6 for FVC in the diagnosis of COPD and other obstructive pulmonary disorders.[10–12] Most of these studies in published literature are retrospective and have used different methods or measurements for FEV1 and FEV6.[5,9–15] Very few studies have been done in India regarding utilization of FEV6 instead of FVC.[16–19] Therefore, we conducted this study with the primary objective to find the utility of FEV1/FEV6 as a surrogate for FEV1/FVC in the diagnosis of COPD in the South Indian population. We also tried to find out the correlation between FEV1/FEV6 ratio and FEV1/FVC ratio to arrive at a fixed cut off value for FEV1/FEV6 ratio as compared to the fixed cut off value of FEV1/FVC in the diagnosis of COPD.

2. Methods

2.1. Study design & subjects

This prospective, cross-sectional study was conducted from January 2017 to November 2018 in a referral academic center for the treatment of pulmonary diseases in southern India. The institutional review board approved the study.

2.2. Inclusion criteria

Patients of 18 years or more presenting to the outpatient department with any of the symptoms suggestive of COPD like progressive and persistent shortness of breath worsening with exertion, chronic intermittent unproductive or productive cough were included into the study.

2.3. Exclusion criteria

Patients with obstructive lung disease other than COPD (e.g. asthma, bronchiectasis), pulmonary disease (e.g. tuberculosis, interstitial lung disease, lung cancer) were excluded from the study. Patients with contraindications for spirometry according to American Thoracic Society guidelines,[20] thoracic surgery in the past six months, acute respiratory infection in the last three weeks, uncontrolled cardiac disease in the last six months (e.g. unstable angina, congestive heart failure, arterial hypertension, arrhythmia), pregnant women were excluded from the study.

2.4. Study procedure

Patients meeting the inclusion and exclusion criteria underwent spirometry. Spirometry was done using Care Fusion Type Master ScreenTM PFT system (2012 make, CareFusion Germany 234 GmbH, Hoechberg, Germany), as per American Thoracic Society guidelines.[21] Both pre and post-bronchodilator values of these parameters were recorded. Post-bronchodilator spirometry was done after nebulizing the patient with salbutamol nebulization solution 2.5 ml (1 ml containing Salbutamol equivalent to 5 mg). COPD was diagnosed as per the GOLD criteria of post-bronchodilator FEV1/FVC <0.70. Three acceptable maneuvers were performed for each spirometry reading, and the spirometry measurement with the largest sum of FEV1 and FVC were chosen for analysis. FEV1, FEV6, FEV1/FEV6 ratio, and FEV1/FVC ratio were also recorded from the best maneuver. The spirometry tests thus obtained were analyzed for their quality and acceptability. The tests not reaching the 6-second expiration time were excluded from the study. The variables recorded from the patients were age, gender, symptoms with their duration, pack-years of smoking, biomass fuel exposure, and family history. The outcome measure recorded were FEV1, FEV6, FVC, pre, and post-bronchodilator FEV1/FEV6 ratio, FEV1/FVC ratio. The details of risk factors, like tobacco smoke, biomass fuel exposure, and family history of COPD were recorded. The calculation of pack-years was done as defined by the National Cancer Institute dictionary.[22] The pack years for patients with a history of bidi smoking were calculated as described by Pal H et al.[23] Bidi is a local cigarette made by rolling coarse tobacco in a dried Coromandel ebony or East Indian ebony leaf (local name temburni or tendu; botanical name: *Diospyros melanoxylon*). The patients were classified into four subgroups based on pulmonary involvement and GOLD guidelines[4]:

Stage 1: FEV1/FVC < 70% and FEV1 ≥ 80%.
Stage 2: FEV1/FVC < 70% and 50% ≤ FEV1 < 80%.
Stage 3: FEV1/FVC < 70% and 30% ≤ FEV1 < 50%.
Stage 4: FEV1/FVC < 70% and FEV1 < 30.

Table 1 – Patient demographic and spirometry characteristics.

PARAMETERS/GOLD STAGE	GOLD 1	GOLD 2	GOLD 3	GOLD 4	TOTAL
Subjects (n; %)	1 (0.8%)	50 (41%)	45 (36.9%)	26 (21.3%)	122 (100%)
Age (years; mean ± SD)	62	60.53 ± 10.2	60.53 ± 10.3	53.08 ± 10.05	57.59 ± 10.47
Male (%)	1 (0.8%)	49 (40.2%)	43 (35.2%)	24 (19.7%)	117 (95.90%)
Female (%)	0 (0%)	1 (0.8%)	2 (1.6%)	2 (1.6%)	5 (4.1%)
Duration of symptom (month; mean ± SD)	12	65.75 ± 49.22	68.8 ± 49.11	71.72 ± 37.56	69.35 ± 46.58
Dyspnoea (n; %)	1 (0.8%)	46 (37.7%)	42 (34.4%)	24 (19.7%)	113 (92.6%)
Cough (n; %)	1 (0.8%)	45 (36.9%)	34 (27.9%)	19 (15.6%)	101 (82.8%)
Wheeze (n; %)	0 (0%)	19 (15.6%)	22 (18%)	10 (8%)	51 (41.8%)
Never Smoker (n, %)	0 (0%)	11 (9%)	8 (6.5%)	2 (1.6%)	21 (17.2%)
Smoker (n, %)	1 (0.08%)	39 (31.9%)	37 (30.3%)	24 (18%)	101 (82.8%)
Pack-Years (years; mean ± SD)	9	8.85 ± 3.31	9.30 ± 4.09	7.66 ± 4.46	8.63 ± 3.49
Pack-Years (%)					
1–10	1 (0.8%)	31 (25.4%)	26 (21.3%)	19 (15.6%)	77 (63.1%)
11–20		8 (6.5%)	19 (15.6%)	5 (4.1%)	24 (17.2%)
Biomass fuel exposure (n, %)	1 (0.8%)	35 (28.7%)	35 (28.7%)	22 (18%)	93 (73.2%)
FEV1 (% Predicted; mean ± SD)	81	61.03 ± 8.15	39.47 ± 5.17	25.8 ± 2.39	46.02 ± 15.61
FEV1/FVC (%; mean ± SD) Pre	59.43	58.24 ± 6.63	54.32 ± 7.9	44.01 ± 5.56	53.15 ± 8.70
FEV1/FVC (%; mean ± SD) Post	65.49	58.53 ± 6.52	52.27 ± 7.4	44.48 ± 6.93	53.39 ± 8.73
FEV1/FEV6(%; mean ± SD) Pre	61.41	59.06 ± 6.85	53.29 ± 7	44.85 ± 5.06	54.24 ± 8.43
FEV1/FEV6(%; mean ± SD) Post	66	59.83 ± 6.53	53.39 ± 7.27	46.44 ± 6.6	54.77 ± 8.37

Abbreviations: COPD- Chronic Obstructive Pulmonary Disease, GOLD- Global Initiative for Chronic Obstructive Lung Disease, FVC- Forced Vital Capacity, FEV1- Forced Expiratory Volume in one second, FEV6- Forced Expiratory Volume in six seconds, SD-standard deviation, Post–Post bronchodilator value.
Table 1: shows general demographic and spirometry outcomes of the patients according to the GOLD staging of COPD.

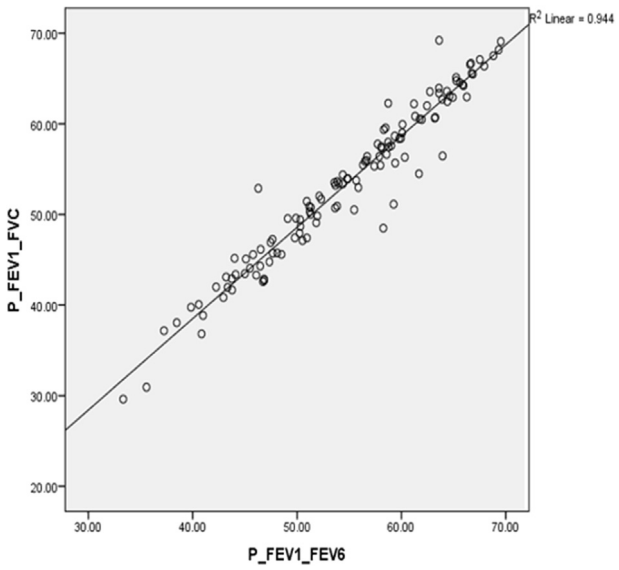

Fig. 1 – Linear Regression line between post-bronchodilator FEV1/FVC and postbronchodilator FEV1/FEV6 ratio showing R^2 value of 0.944; X axis: FEV1/FEV6, Y axis.

2.5. *Methods of statistical analysis*

Considering an expected sensitivity of 98% and specificity of 94% with the expected prevalence of COPD as 30% by spirometry (institute data), using the statistical formula for estimating a population proportion a sample size of 122 was calculated (95% confidence interval and 5% absolute precision). Statistical package for social sciences (IBM SPSS) version 19.0 was used for statistical analysis. The normality of the data was tested by a one-sample Kolmogorov–Smirnov test. The distribution of data for categorical variables and ordinal data such as gender, symptoms, presence of smoking, history of exposure to biomass fuel was expressed as percentages and frequencies. Continuous parametric data were expressed as mean and standard deviation. Continuous non-parametric data were expressed as median with range. Correlation between various variables was analyzed using Pearson's correlation analysis. Linear regression analysis was used to analyze the relationship between various variables such as FEV1/FVC ratio and FEV1/FEV6 ratio. All statistical tests were carried out at a 5% level of significance and p-value <0.05 was considered as statistically significant.

3. Results

Five hundred forty patients were suspected clinically for COPD and underwent spirometry test. One hundred and twenty-two patients satisfied GOLD diagnostic criteria of FEV1/FVC <0.7 and were diagnosed as COPD. There were 117 (95.9%) males and 5 females (4.1%) in the study. Most of the patients (91, 74.6%) were above 50 years of age. Ninety-three percent of patients (114/122) had 2 or more symptoms at presentation. The most common risk factor for COPD was smoking (n = 101, 82.8%) followed by Biomass fuel exposure (n = 93,73.2%). Most of the male patients (84/117, 71.8%) had exposure to both biomass fuel and smoking. The mean smoking history was 8.63 (SD ± 3.49) pack years. Almost two-thirds of them had a 1–10 pack-years history of smoking. Patients were classified based on their post-bronchodilator FEV1 values into various

Table 2 – Shows Cut-off values for FEV1/FEV6 found in various studies ([14–16,25,26,28,29,30]).

Study	Country	Year	Number of subjects	Correlation coefficient	Cut-off of FEV1/FEV6 ratio
Current study	India	2016–18	122	0.972	0.72
Frith et al (26)	Australia	2011	204	0.72	0.75
Ching et al (16)	Malaysia	2015–16	117	0.636	0.75
Rosa et al (28)	Brazil	2007	963	0.92	0.75
Wang et al (29)	China	2016	767	0.954	0.72
COPD Gene trial (14)	United States	2013	10,018	0.90	0.73
Singh and Lohia (25)	India	2008–09	467	0.93	0.73
Aghili et al (15)	Iran	2013	318	Not Studied	0.71
Melbye et al (30)	Norway	2006	3874	0.86	0.73

GOLD grades for the severity of obstruction. There were 50 (41%) and 71 (58.2%) patients in GOLD category 2 (moderate) and 3 & 4 (severe and very severe) respectively. The demographic and spirometry outcomes are presented in Table 1.

3.1. *Spirometry correlation*

There was a significant correlation ($r = 0.972$, $P < 0.01$) between post bronchodilation FEV1/FVC and FEV1/FEV6 ratios (Fig. 1). The relationship between the post-bronchodilator FEV1/FVC and FEV1/FEV6 ratios (linear regression analysis) was found to be FEV1/FVC = −1.845 + 1.009(FEV1/FEV6). Using this formula, the post-bronchodilator FEV1/FEV6 value of 71.845 ($p < 0.01$) was obtained corresponding to the post-bronchodilator FEV1/FVC value of 70.00 for the diagnosis of COPD.

We could not find any statically significant correlation between Post Bronchodilation FEV1/FVC and pack years smoking ($r = -0.136$, p-value 0.135) or duration of symptoms ($r = -0.078$, p-value 0.394).

Post Bronchodilator FEV1/FEV6 had both sensitivity and specificity of 100% when compared to Post bronchodilator FEV1/FVC of 0.70 for diagnosing COPD. The positive predictive value, as well as negative predictive value, were 100%.

4. Discussion

We found a positive correlation between post-bronchodilator FEV1/FVC and FEV1/FEV6 ratios in the present study which demonstrate that FEV1/FEV6 should be used as a surrogate for FEV1/FVC in the diagnosis of COPD. A positive correlation coefficient ranging from 0.636 to 1.0 for the FEV1/FVC and FEV1/FEV6 ratios has been reported by different investigators.[5,14,16,24–30] We obtained a post-bronchodilator FEV1/FEV6 value of 71.845 ($p < 0.01$) corresponding to the post-bronchodilator FEV1/FVC value of 70.00 for diagnosis of COPD. The findings of our study are like other published studies.[5,14,16,24–30] A comparative analysis of cut-off values and correlation is given in Table 2. In the COPD Gene trial by Bhatt et al, a Cohen's Kappa coefficient of 0.90 ($p < 0.001$) between the two ratios was found, indicating a good agreement.[14] The investigators reported that the FEV1/FEV6 cut-off value of 0.73 was significantly associated with COPD Quality of life, functional indices, and CT measures of emphysema and found it to be superior to FEV1/FVC in predicting future exacerbations and COPD related morbidity.[14] Enright and colleagues found that FEV1/FEV6 can be used to predict lung function decline over time.[31] They further stated that the shorter duration of the FEV6 maneuver was easy to perform and the FEV1/FEV6 ratio is a good substitute for the FEV1/FVC for the screening of smokers for the presence of airflow obstruction. A meta-analysis by Jing et al. concluded that FEV1/FEV6 is a sensitive and specific test for the diagnosis of airway obstruction and can be used as a valid alternative for the FEV1/FVC in the diagnosis of airway obstruction.[32]

Most of the studies done were retrospective in nature and analysed spirometry data of studies with different aims and objectives to start with.[5,10,13–18] While accessing the correlation between two ratios either two separate efforts or instruments or the different operators were used by several studies. Ching et al. used a small handheld device (COPD-6™) for FEV1/FEV6 measurement and office spirometry for the FVC maneuver and hence could not find a strong agreement between the two ratios ($r = 0.634$).[16] Similarly, Firth et al. used handheld expiratory flow meter (PiKo-6®, nSpire Health, Inc.) to assess the validity of the instrument and used FEV6 values from the same instrument and FVC maneuver from a different office spirometer (EasyOne®; ndd Medical Technologies, Andover, MA, USA) and found a correlation coefficient of 0.72.[26] Lundgren et al. used prebronchodilator values hence their finding did not address its utility in the diagnosis of COPD, which requires a Post Bronchodilator Value.[33]

The strength of our study was its prospective nature and all spirometric measurements were done by a single trained operator using single machine and all the values were taken from the single best effort, thus avoiding the effort to effort variation. Spirometry results were analyzed for their quality and acceptability.

4.1. *Limitations*

This was a single-center study done in south India hence our findings might not fit for the rest of the Indian population. As most of the subjects were males and smokers, the generalization of the results to non-smokers and females is doubtful.

5. Conclusion

This prospective cross-sectional study demonstrated a positive correlation coefficient ($r = 0.972$, $p < 0.01$) between the post-bronchodilator FEV1/FEV6 and FEV1/FVC ratios and a cut off value of 71.845 for the post-bronchodilator FEV1/FEV6 ratio ($p < 0.01$), which should be used as fixed diagnostic criteria for

COPD. Thereby, we conclude that the FEV1/FEV6 ratio should be used as a surrogate for the FEV1/FVC ratio in the diagnosis of Chronic Obstructive Pulmonary Disease. The specific use of the FEV1/FEV6 ratio for the diagnosis of COPD has the advantage of a fixed cut-off time and easier for the patient to perform.

With the validation of several handheld devices to measure the FEV6, now is the time to derive reference values and to arrive at a consensus for a fixed cut-off value of FEV1/FEV6 for the diagnosis of COPD.

Presentation at a meeting

NAPCON 2018 at Ahmedabad, India.

Conflicts of interest

The authors have none to declare.

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