ORIGINAL ARTICLE

Comparison between FEV_1/FEV_6 and FEV_1/FVC as screening of chronic obstructive pulmonary disease

Ng Seow Ching, MRCP, Mohd Faizul Bin Abu Samah, MRCP, Khaled Mohamed Helmy Abd El-Aziz, Egyptian Higher DP Speciality of Chest Diseases, Sia Koon Ket, Fellowship in Gastroenterology

Medical Department, Hospital Tuanku Fauziah, Jalan Kolam, Kangar, Perlis Indera Kayangan, Malaysia

ABSTRACT

Objective: To compare FEV_1/FEV_6 to the standard spirometry (FEV_1/FVC) as a screening tool for COPD.

Methods: This cross-sectional study was conducted at Hospital Tuanku Fauziah, Perlis, Malaysia from August 2015 to April 2016. FEV_1/FEV_6 and FEV_1/FVC results of 117 subjects were analysed. Demographic data and spirometric variables were tabulated. A scatter plot graph with Spearman's correlation was constructed for the correlation between FEV_1/FEV_6 and FEV_1/FVC. The sensitivity, specificity, positive and negative predictive values of FEV_1/FEV_6 were determined with reference to the gold standard of FEV_1/FVC ratio <0.70. Receiver-operator characteristic (ROC) curve analysis and Kappa statistics were used to determine the FEV_1/FEV_6 ratio in predicting an FEV_1/FVC ratio <0.70.

Results: Spearman's correlation with r = 0.636 (P<0.001) was demonstrated. The area under the ROC curve was 0.862 (95% confidence interval [CI]: 0.779 - 0.944, P<0.001). The FEV_1/FEV_6 cut-off with the greatest sum of sensitivity and specificity was 0.75. FEV_1/FEV_6 sensitivity, specificity, positive and negative predictive values were 93.02%, 67.74%, 88.89% and 77.78% respectively. There was substantial agreement between the two diagnostic cut-offs (κ = 0.634; 95% CI: 0.471 - 0.797, P<0.001)

Conclusions: The FEV_1/FEV_6 ratio can be considered to be a good alternative to the FEV_1/FVC ratio for screening of COPD. Larger multicentre study and better education on spirometric techniques can validate similar study outcome and establish reference values appropriate to the population being studied.

KEY WORDS:
FEV_1/FEV_6, FEV_1/FVC, chronic obstructive pulmonary disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterised by persistent and progressive airflow limitation, and is associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. It is an important and still-increasing cause of morbidity and mortality worldwide and results in substantial burden to the health care economy. In fact, COPD is projected to be the fourth leading cause of death worldwide by the year 2030.[1]

The criteria for the diagnosis of COPD as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) remains the spirometric criterion of a post-bronchodilator fixed ratio of FEV_1/FVC <0.70. Patients whose spirometry confirm the diagnosis of COPD will go for combined assessment and one element of assessment is the airway limitation based on FEV_1 versus predicted values and will be further classified into (FEV_1 ≥80% predicted), GOLD 2 (50%≤ FEV_1 <80% predicted), GOLD 3 (30%≤ FEV_1 <50% predicted), and GOLD 4 (FEV_1 <30% predicted).[1] Unfortunately, spirometry is not widely available in most health care clinics in Malaysia. The sophistication of spirometers translates to a need for specialised technicians to perform the examination. Spirometry requires a prolonged exhalation time to achieve a plateau on the volume-time curve, and this can lead to exhaustion and possible syncope in test subjects.[2]

The National Lung Health Education Program recommended the use of FEV_1/FEV_6 for the detection of COPD in 2000.[3] This statement was supported by several studies that concluded that FEV_1/FEV_6 has high sensitivity and specificity compared to the gold standard of FEV_1/FVC in the screening for COPD.[4-17] The use of FEV_1/FEV_6 simplifies testing procedures and reduces test variability, which helps to improve its diagnostic accuracy.[18] The criteria adopted by published studies to define obstruction from FEV_1/FEV_6 are variable. Several studies defined obstruction from FEV_1/FEV_6 based on lower limits of normality (LLN) developed from the third National Health and Nutrition Examination Survey (NHANES III) reference equations.[4,9,10,12] These reference equations are influenced by age, sex, height and ethnicity and are currently available only for the USA population (NHANES III survey)[19] and for European subjects in the 65 to 85 years age group.[20] Other studies used the sensitivity and specificity values associated with receiver operator characteristic (ROC) curve analysis to find the best cut-off point for FEV_1/FEV_6 comparable to GOLD FEV_1/FVC fixed ratio of <0.70.[5,13-17]

OBJECTIVE

To demonstrate the reliability of FEV_1/FEV_6 as a screening tool for COPD in general practice compared to the standard spirometry which is FEV_1/FVC.

This article was accepted: 8 October 2017
Corresponding Author: Ng Seow Ching
Email: xuiayushiching@gmail.com

MATERIALS AND METHODS

Study Design and Subjects

This was a cross-sectional study conducted from August 2015 to April 2016. A total of 117 subjects referred to Chest Clinic, Hospital Tuanku Fauziah for spirometry from Medical Outpatient Department (MOPD) and health care clinics to confirm the diagnosis of COPD were recruited into the study. The inclusion criteria were age more than 40 years old; history of dyspnoea that was progressive, persistent and characteristically worsened with exercise; history of chronic cough (may be intermittent or unproductive); history of chronic sputum production of any kind; history of exposure to risk factors (tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals); and any smoker even in the absence of above symptoms. Subjects who were contraindicated for spirometry as per American Thoracic Society/European Respiratory Society recommendations[2] and subjects who were anticipated to be unable to perform six forced blows as presumed by the spirometry technician were excluded from the study. This study was registered with National Medical Research Register with the reference number of NMRR-15-963-26480 (IIR) and was approved by Medical Research & Ethics Committee, Ministry of Health, Malaysia.

Instruments

COPD-6 is a small portable electronic device that is powered by two disposable batteries. It has a large easy-to-read display and can display on a colour scale the degree of airway obstruction according to the GOLD classification. The device also has an automatic test quality alert that detects errors such as premature ending of the manoeuvre or cough. The device requires only minimal instruction for use by non-respiratory specialists.[21] The COPD-6 device was checked for calibration errors before the start of the study by the investigators. Before taking any readings with the device, the trained staff entered patient's data including age, sex, height and weight. Height was measured to the nearest centimetre without shoes and weight was recorded to the nearest kilogram. Three post-bronchodilator readings (i.e., 15 minutes after the application of 400mcg of aerosolised salbutamol via a spacer) were taken. The highest FEV_1 and FEV_6 value of the three post-bronchodilator measurements was used and the FEV_1/FEV_6 ratio was calculated.

Conventional spirometry was performed with a PC-based SpiroPerfect Spirometer (Welch Allyn, New York, NY, USA) by highly trained and experienced technicians in accordance with American Thoracic Society criteria.[22] The spirometer was calibrated daily using a 3L syringe. The spirometry tests obtained were analysed by the investigators for their quality and acceptability. Three acceptable and reproducible manoeuvres were performed in each test, and the spirometric measurements with the highest FEV_1/FVC ratio were chosen for final analysis. A post-bronchodilator fixed ratio of $FEV_1/FVC < 0.70$ was used as criteria for the diagnosis of COPD as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1]

Statistical Analysis

Sample size calculation was done using Raosoft Sample Size Calculator version 2004 (http://www.raosoft.com/samplesize.html). With a margin of error of 8%, a confidence level of 90%, a response distribution of 50%, and to account for 10% drop outs, a total sample size of 117 subjects was enrolled for this study. Demographic data was tabulated using Microsoft Excel 2007 (Microsoft Corp). Age, height, weight, smoking pack years and years of environmental/occupational exposure were reported as means ± SD. A scatter plot graph was constructed and Spearman's correlation was used to study the correlation between FEV_1/FEV_6 and FEV_1/FVC. The performance of the FEV_1/FEV_6 was analysed using two-by-two tables, to determine the sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV). Receiver operator characteristic (ROC) curve analysis was performed to measure the accuracy of FEV_1/FEV_6 in comparison with FEV_1/FVC, and to identify the FEV_1/FEV_6 cut-off that had the greatest sum of sensitivity and specificity for the diagnosis of COPD as defined by FEV_1/FVC ratio <0.70. The agreement between FEV_1/FEV_6 and FEV_1/FVC was also calculated using Kappa statistics. All analyses were performed using Statistical Package for the Social Sciences (SPSS v23).

RESULTS

Of the total 117 subjects, 86.3% were males and 13.7% were females. The majority of subjects were Malays (88%). Smoking status analysis revealed that 41% of subjects were current smokers, 47.9% were former smokers, 1.7% was never smokers, and 9.4% had history of environmental/occupational exposure to risk factors (mainly exposure to home cooking and heating fuels, with one of the subject being a worker in curtain production industry). Subject characteristics and mean spirometric results are shown in Table I.

Before the analysis of accuracy, a scatter plot graph between FEV_1/FEV_6 and FEV_1/FVC ratios was constructed, and Spearman's correlation with $r = 0.636$ ($P<0.001$) was found (Figure 1).

Considering FEV_1/FVC ratio <0.70 as being the gold standard to diagnose COPD, a receiver operator characteristic (ROC) curve was constructed to determine the best corresponding cut-off for FEV_1/FEV_6 (Figure 2). The area under the ROC curve was 0.862 (95% confidence interval (CI): 0.779 to 0.944, $P<0.001$). The FEV_1/FEV_6 cut-off, corresponding to the greatest sum of sensitivity and specificity, was 0.75. For the study group, the FEV_1/FEV_6 sensitivity was 93.02% and specificity was 67.74%. The PPV of FEV_1/FEV_6 was 88.89%, and the NPV was 77.78% (Table II). Diagnostic accuracy of FEV_1/FEV_6 across different cut-off points was shown in Table III. As the cut-off point was lowered, FEV_1/FEV_6 became less sensitive but more specific, the PPV increased, and the NPV decreased.

Table I: Characteristics of the Study Group

Characteristic	Values
Age (years; mean ± SD)	67.38 ± 11.58
Male (%)	86.3
Ethnicity (%)	
Malay	88
Chinese	9.4
Siamese	2.6
Weight (kg; mean ± SD)	60.79 ± 14.21
Height (cm; mean ± SD)	159.18 ± 7.68
Smoking Status (%)	
Current Smoker	41
Former Smoker	47.9
Never Smoker	1.7
Environmental/Occupational Exposure	9.4
Pack-Years (mean ± SD)	37.97 ± 14.51
Pack-Year Categories (%)	
1 – 14	5
15 – 24	18
25 – 49	52
50+	25
FEV_1/FVC (%; mean ± SD)	57.37 ± 16.44
FEV_1/FEV_6 (%; mean ± SD)	61.70 ± 17.00

Table II: Comparison of FEV_1/FEV_6 with FEV_1/FVC for the Diagnosis of COPD

FEV_1/FEV_6	FEV_1/FVC		Total
	< 70%	≥ 70%	
< 75%	80	10	90
≥ 75%	6	21	27
Total	86	31	117

Sensitivity: 93.02%; specificity: 67.74%; positive predictive value: 88.89%; negative predictive value: 77.78%; using FEV_1/FVC <70% as a fixed cut-off; using FEV_1/FEV_6 <75% as a fixed cut-off.

Table III: Diagnostic Accuracy of FEV_1/FEV_6 across Different Cut-Off Points. PPV: Positive Predictive Value; NPV: Negative Predictive Value

FEV_1/FEV_6(%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
< 70	80.23	77.42	90.79	58.54
< 73	87.21	70.97	89.29	66.67
< 75	93.02	67.74	88.89	77.78
< 78	94.19	64.52	88.04	80.00
< 80	96.51	54.84	85.57	85.00

Overall agreement between FEV_1/FEV_6 and FEV_1/FVC was assessed using kappa statistics. A kappa value of 0.634 (95% CI = 0.471 – 0.797, P< 0.001) was obtained, indicating substantial agreement between FEV_1/FEV_6 and FEV_1/FVC.

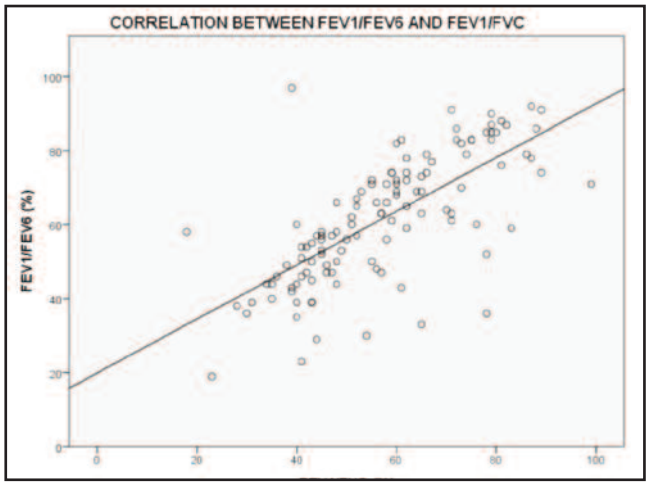

Fig. 1: Correlation between FEV_1/FEV_6 and FEV_1/FVC.

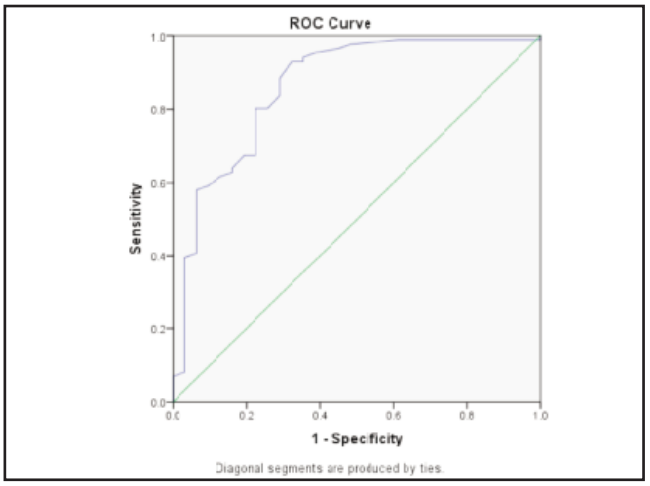

Fig. 2: Receiver operator characteristic (ROC) curve for FEV_1/FEV_6 using FEV_1/FVC ratio < 0.70 as gold standard to diagnose COPD. Area under the ROC curve = 0.862 (95% confidence interval: 0.779 – 0.944, P<0.001).

DISCUSSION

FEV_6 has already been demonstrated to be a reliable alternative for FVC in identifying obstructive and restrictive spirometric patterns, using the NHANES III reference equations to calculate LLN for each spirometric index.[4,7] However, these studies were limited by using only pre-bronchodilator values and the study samples only contained Caucasians. Besides, reference equations developed from NHANES III are currently available only for the USA population.[19] Garcia-Rio F et al.[20] had also published spirometric reference equations for European subjects aged 65 to 85 years old. There is currently no available spirometric reference equations developed for use in Asian population.

Several studies examined the possibility of establishing a fixed cut-off for FEV_1/FEV_6 that corresponds to the GOLD FEV_1/FVC fixed ratio of <0.70.[5,13-17] The advantage of using a fixed cut-off value for the FEV_1/FEV_6 ratio to diagnose airway obstruction was highlighted by the main COPD guidelines.[3,23] Four studies showed a similar cut-off point (0.73) of the FEV_1/FEV_6 ratio for the detection of airway obstruction.[13-15,17] Two other studies however showed another similar cut-off point (0.75) of the FEV_1/FEV_6 ratio.[5,16] Our study showed that the best cut-off for FEV_1/FEV_6 was 0.75, corresponded to the studies by Rosa FW et al.[5] and P. Frith et al.[16] While fixed cut-off values are more widely used, there is potential for misclassification, as spirometric indices are highly influenced by age, sex, race and height. For example, elderly subjects typically show an age-related decline in FEV_1/FVC and FEV_1/FEV_6, causing a significant over-diagnosis of airway obstruction.[24] Thus, fixed cut-off values should be used with caution, particularly outside the middle-aged population.

The use of six-second expiratory manoeuvres provide several advantages over measurements of FVC in the elderly and in primary care.[3,18] FEV_6 is less demanding for patients as patients do not have to force expire through a 15- to 20-second period, thus making the manoeuvre more easily achievable especially in the elderly and impaired patients. The shorter expiratory times require less data storage space, hence the ability to develop smaller and portable spirometers which is convenient for use in primary care setting. In addition, despite minimal instructions provided to non-respiratory specialists, these expiratory flow meters have high accuracy and reliability in the detection of airflow obstruction. This can facilitate the identification and referral of patients who are likely to benefit from formal spirometric evaluation in specialised respiratory institutions.

Our study showed a sensitivity of 93.02% but specificity of 67.74%, using the fixed cut-off FEV_1/FEV_6 <0.75. The kappa agreement between FEV_1/FEV_6 and FEV_1/FVC in our study was 0.634, indicating only substantial agreement between the two tests. Analysis of the discordant cases showed that there were discrepancies in the subjects' techniques in performing on the COPD-6 and conventional spirometer. Hence, we felt that more education can be given to patients on the proper techniques of performing on the COPD-6 and conventional spirometer. As our study was a pilot study involving only a small number of subjects, this may not represent the whole Malaysian COPD population and we recommend that larger scale study involving specialised respiratory institutions and primary care centers to be conducted in Malaysia, so as to get a more accurate outcome of study that better reflect our local context.

CONCLUSION

We thereby conclude that FEV_1/FEV_6 fixed ratio can be considered a good alternative to FEV_1/FVC ratio in the screening of COPD. Better education to patients on proper respiratory manoeuvres and larger multi-centre studies are required to validate similar study outcome and to establish reference values that are technically and biologically appropriate to the population being studied.

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this paper.

REFERENCES

1. Global Strategy for Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 [Updated Dec 2015, cited July 2016]. Available from: http://www.goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/.
2. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R et al. General considerations for lung function testing. Eur Respir J 2005; 26(1): 153-61.
3. Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000; 117(4): 1146-61.
4. Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV6 is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med 2000; 162(3 Pt 1): 917-9.
5. Rosa FW, Perez-Padilla R, Camelier A, Nascimento OA, Menezes AM, Jardim JR et al. Efficacy of the FEV1/FEV6 ratio compared to the FEV1/FVC ratio for the diagnosis of airway obstruction in subjects aged 40 years or over. Braz J Med Biol Res 2007; 40(12): 1615-21.
6. Enright PL, Connett JE, Bailey WC. The FEV1/FEV6 predicts lung function decline in adult smokers. Respir Med 2002; 96(6): 444-9.
7. Vandevoorde J, Verbanck S, Schuermans D, KartounianJ, Vincken W. FEV1/FEV6 and FEV6 as an alternative forFEV1/FVC and FVC in the spirometric detection of airway obstruction and restriction. Chest 2005; 127(5): 1560-4.
8. Lundgren FL, Cabral MM, Climaco DC, de Macedo LG, Coelho Mde A, Dias AL. Determination of the efficacy of FEV6 as a surrogate for FVC in the diagnostic screening for chronic obstructive pulmonary disease through the comparison of FEV1/FVC and FEV1/FEV6 ratios. J Bras Pneumol 2007; 33(2): 148-51.
9. Lamprecht B, Schirnhofer L, Tiefenbacher F, Kaiser B, Buist SA, Studnicka M et al. Six-second spirometry for detection of airway obstruction: a population-based study in Austria. Am J Respir Crit Care Med 2007; 176(5): 460-4.
10. Akpinar-Elci M, Fedan KB, Enright PL. FEV6 as a surrogate for FVC in detecting airways obstruction and restriction in the workplace. Eur Respir J 2006; 27(2): 374-7.
11. Gleeson S, Mitchell B, Pasquarella C, Reardon E, Falsone J, Berman L. Comparison of FEV6 and FVC for detection of airway obstruction in a community hospital pulmonary function laboratory. Respir Med 2006; 100(8): 1397-1401.
12. Perez-Padilla R, Wehrmeister FC, Celli BR, Lopez-Vrela MV, Montes de Oca M, Muino A et al. Reliability of FEV1/FEV6 to Diagnose Airflow Obstruction Compared with FEV1/FVC: The PLATINO Longitudinal Study. PLoS ONE 8(8): e67960.
13. Vandevoorde J, Verbanck S, Schuermans D, KartounianJ, Vincken W. Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV1/FEV6 and FEV6. Eur Respir J 2006; 27(2): 378-83.
14. Melbye H, Medbo A, Crockett A. The FEV1/FEV6 ratio is a good substitute for the FEV1/FVC ratio in the elderly. Prim Care Respir J 2006; 15(5): 294-8.

15. Kumar Singh A, Lohia A. FEV1/FEV6: a reliable, easy-to-use, and cheaper alternative to FEV1/FVC in diagnosing airway obstruction in Indian population. ISRN Pulmonology. Volume 2012 (2012):109295.
16. P. Frith, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A et al. Simplified COPD Screening: Validation of the PiKo-6® in Primary Care. Prim Care Respir J 2011; 20(2): 190-8.
17. Bhatt SP, Kim YI, Wells JM, Bailey WC, Ramsdell JW, Foreman MG et al. FEV1/FEV6 to diagnose airflow obstruction: comparisons with computed tomography and morbidity indices. Ann Am Thorac Soc 2014; 11(3): 335-41.
18. Jing JY, Huang TC, Cui W, Xu F, Shen HH. Should FEV1/FEV6 replace FEV1/FVC ratio to detect airway obstruction? A metaanalysis. Chest 2009; 135(4): 991-8.
19. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S population. Am J Respir Crit Care Med 1999; 159(1): 179-87.
20. Garcia-Rio F, Pino JM, Dorgham A, Alonso A, Villamor J. Spirometric reference equations for European females and males aged 65–85 yrs. Eur Respir J 2004; 24(3): 397-405.
21. Vitalograph® Your cardio-respiratory partner [Cited July 2016]. Available from: https://vitalograph.co.uk/product/161419/copd-6.
22. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995; 152(3): 1107-36.
23. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23(6): 932-46.
24. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J 2002; 20(5): 1117-22.