

Research Article



Diagnostic Performance of Forced Expiratory Volume in Six Seconds for the Detection of Obstructive and Restrictive Pulmonary Diseases in a Population of Young Adults in South of Iran

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Abstract

Background: Forced expiratory volume in 6 seconds (FEV6) is a reliable substitute for forced vital capacity (FVC) to identify pulmonary diseases. This study aimed to determine the diagnostic performance of FEV6 in the detection of obstructive and restrictive spirometric patterns.

Methods: In this cross-sectional study, spirometry was performed on patients referred to the occupational medicine clinic of Shahid Mohammadi Hospital, Bandar Abbas, Iran, 2018. Spirometric parameters, including FEV1, FVC, and FEV6, were recorded for those tests meeting the American Thoracic Society (ATS) standards. Taken as the reference, the FEV1/FVC ratio < 70% indicated airway obstruction, and the restrictive pattern was defined as FVC < 80%.

Results: In general, 1100 spirometries were included after meeting the ATS standards. The optimal cut-off of FEV1/FEV6 for the prediction of airway obstruction was 71.45% with a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of 97.22%, 98.22%, 89.17%, 99.57%, and 98.09%, respectively. The best cut-off of FEV6 for the prediction of the restrictive pattern was 79.23% with the corresponding diagnostic indices of 97.29%, 99.05%, 94.11%, 99.57%, and 98.81%, respectively. Based on the FEV1/FEV6 cut-off, the frequency of obstruction was 14.27% (157/1100) compared to 13.09% based on FEV1/FVC. The frequency of restriction was 13.90% (153/1100) according to the FEV6 cut-off compared to 13.45% with respect to FVC.

Conclusion: Overall, our results indicated the applicability of FEV1/FEV6 as an accepted surrogate for FEV1/FVC to diagnose airway obstruction, particularly to screen for chronic obstructive pulmonary disease (COPD) among high-risk patients. In addition, FEV6 is potentially an appropriate substitute for FVC to detect a restrictive pattern.

Keywords: Forced expiratory volume, Sensitivity and specificity, Airway obstruction, Airway restriction

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Background

Chronic obstructive pulmonary disease (COPD) is a significant public health problem, which can lead to mortality and is estimated to become the third leading cause of mortality by 2020. COPD, which can be prevented and treated, is a prevalent respiratory disorder with persistent airflow limitations (commonly progressive) due to airway and/or alveolar dysfunction owing to prolonged exposure to noxious particles or gases (1). The available consensus instructions, including the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program, emphasize the significance of the early diagnosis of COPD even in the preclinical stage. Therefore, successful cessation of exposure, which is a cost-effective intervention, prevents further disease

progression. Spirometry is the “gold standard” for the diagnosis of COPD (1, 2). COPD is considered by the GOLD as an irreversible disorder detected when the forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) is constantly lower than 70% after bronchodilator administration. Further, an FVC of lower than 80% in an acceptable FEV1/FVC ratio is regarded as restrictive pulmonary disease. However, the result of spirometric measurements considerably depends on consistent attempts made by patients and technicians (3). For a proper and logical FVC, two criteria are used to end the test, including when patients are unable or must not continue exhalation and when a fixed volume-time curve is required during a minimum of one second (≤ 1) (< 0.025 l), with patients aged 10 years or older required

to continue exhalation for 6 seconds or longer (and those younger than 10 years for 3 seconds or longer) (4). Forced expiratory volume in 6 seconds (FEV6) is considered a substitute for FVC (4-7). The advantages of FEV6 have been demonstrated to be easy applicability (for both patients and technicians) (8), reduced total duration of spirometry test, no restriction regarding accuracy to detect extremely low flows at the final stage, and decreased spirometry complications such as syncope (2, 9). Nonetheless, no universal reference cut-off is available for FEV6 (10, 11). Moreover, although some FEV1/FEV6 cut-offs have been established in studies from different countries to serve as FEV1/FVC < 70%, recommended by GOLD standards (12), they may not be applicable to other populations due to variations in age, race, height, and weight (5, 6). In addition, no research has calculated multilevel risk ratios of FEV1/FEV6 that can promote its applicability.

Objectives

This research aimed at determining fixed cut-offs for FEV1/FEV6 and FEV6 to diagnose airway obstructive and restrictive patterns in a population of young adults in the south of Iran, as well as evaluating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of these cut-offs for the detection of airway obstruction and restriction in this population.

Methods

The present cross-sectional study included patients referred to the occupational medicine clinic of Shahid Mohammadi Hospital in Bandar Abbas, Iran during 2018. Patients were recruited through census sampling, and written informed consent was obtained from all of them. The exclusion criteria were contraindications of spirometry including blood pressure exceeding 180/100 mm Hg, pulmonary tuberculosis or any other contagious respiratory diseases, history of myocardial infarction or unstable angina, evidence of respiratory distress, and any abnormality in the physical examination of the respiratory system. The other criteria included active hemoptysis, thoracic or abdominal aortic aneurysm, recent stroke, recent eye or ear surgery (within previous 6 weeks), recent thoracic or abdominal surgery (within previous 6 weeks), and inability to continue exhalation for 6 seconds. The spirometries were performed by experienced technicians using the "Viasys Health, Master Scope version 4.6" spirometer (Care, Hoechberg, Germany) based on the American Thoracic Society (ATS) instructions (13). The spirometry tests were evaluated by the researchers in terms of repeatability and acceptability. Three accepted maneuvers were conducted for every spirometric reading, and the one with the best spirometric assessment and the highest FEV1 and FVC (taken together) was considered as the final assessment. FEV6 was obtained as well. Tests

that did not reach the 6-second expiratory time were excluded from the examination. Spirometry parameters, including FEV1/FEV6, FEV6, FEV1/FVC, and FVC, were recorded and compared with the lower limit of normal (LLN) data (14). In patients with COPD, based on the GOLD standards (FEV1/FVC < 70%), the FEV1/FEV6 values were used to draw a *receiver operating characteristic* (ROC) curve determining the sensitivity and specificity of its optimal cut-off point. Furthermore, in patients with normal FEV1/FVC and FVC < 80% (restrictive lung disease), the best cut-off of FEV6 was determined through the ROC curve. PPV, NPV, and diagnostic accuracy were calculated for both cut-offs. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.), and *P* values ≤ 0.05 were considered statistically significant.

Results

Baseline Data

The results of 1113 consecutively conducted spirometry tests were available. Thirteen tests were excluded due to failure to achieve the expiration duration of 6 seconds. Therefore, data from 1100 middle-aged cases (88.4% male, 11.6% female) were assessed, and the participants were aged 18-76 years with a mean age of 37.22 (± 8.95). Table 1 provides the subjects' baseline information. The GOLD guideline was applied for the detection of patients with restrictive lung disease via spirometry. According to the GOLD criteria, participants were assigned to the following subgroups regarding the level of obstruction (15):

Stage 1: FEV1/FVC < 70% and FEV1 ≥ 80%

Phase 2: FEV1/FVC < 70% and 50% ≤ FEV1 < 80%

Phase 3: FEV1/FVC < 70% and 30% ≤ FEV1 < 50%

Phase 4: FEV1/FVC < 70% and FEV1 < 30%

Spirometric Diagnosis of Obstructive and Restrictive Patterns

The optimal cut-off of FEV1/FEV6 for the prediction of airway obstruction was 71.45% (Figure 1) with a sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 97.22, 98.22, 89.17, 99.57, and 98.09% respectively. Twenty-one cases were incorrectly diagnosed using FEV1/FEV6, including 4 false negatives and 17 false positives. Based on the FEV1/FEV6 cut-off, the frequency of obstruction was 14.27% (157/1100) compared to 13.09% based on FEV1/FVC (Table 2). The best FEV6 cut-off for the prediction of the restrictive pattern was 79.23% (Figure 2) with the corresponding diagnostic indices of 97.29, 99.05, 94.11, 99.57, and 98.81%, respectively. Thirteen cases were incorrectly diagnosed using FEV6, including 4 false negatives and 9 false positives. The frequency of restriction was 13.90% (153/1100) based on the FEV6 cut-off compared to 13.45% with respect to FVC (Table 3).

Discussion

Table 1. Demographic Information, Restriction, and Obstruction and its Level in the Participants

	Number	Age (y)	Height (cm)	Weight (kg)	Obstruction						
		Mean ± SD	Mean ± SD	Mean ± SD	Normal	Restriction	Stage 1	Stage 2	Stage 3	Stage 4	Total
Male	972	37.41 ± 9.06	174.3 ± 6.48	77.71 ± 14.47	701	139	54	78	3	0	135
Female	128	35.38 ± 7.62	161.18 ± 6.25	65.91 ± 13.79	107	9	2	7	0	0	9
Total	1100	37.22 ± 8.95	172.79 ± 7.67	76.33 ± 14.84	808	148	56	85	3	0	144
					73.45 (%)	13.45 (%)	5.09 (%)	7.74 (%)	0.27 (%)	0 (%)	13.1 (%)

Note. SD: Standard deviation.

Table 2. Cross-tabulation of FEV1/FEV6 and FEV1/FVC for Detecting Airway Obstruction

Index	FEV1/FVC		Total
	Obstruction	No Obstruction	
FEV1/FEV6	Obstruction	140	157
	No obstruction	4	943
	Total	144	1100

Note. Values are expressed as numbers. FEV1: Forced expiratory volume in 1 second; FEV6: Forced expiratory volume in 6 seconds; FVC: Forced vital capacity.

Table 3. Cross-tabulation of FEV6 and FVC for Detecting Airway Restriction

Index	FVC		Total
	Restriction	No Restriction	
FEV6	Restriction	144	153
	No restriction	4	947
	Total	148	1100

Note. Values are expressed as numbers. FEV6: Forced expiratory volume in 6 seconds; FVC: Forced vital capacity.

FEV6 is an appropriate surrogate for FVC in identifying obstructive and restrictive spirometric patterns (16). The current study sought to determine the optimal cut-offs of FEV6 and FEV1/FEV6 in the detection of restrictive and obstructive pulmonary diseases using the ROC curve. However, cut-off points should be used cautiously as the spirometer indices can be highly affected by demographic factors such as age, gender, height, and race. Our results revealed that FEV1/FEV6 < 71.45% is a proper substitute for FEV1/FVC < 70% to detect airway obstruction and FEV6 < 79.23% can be applied as a suitable surrogate for FVC < 80% to detect restrictive spirometric patterns in adults.

Previous studies have demonstrated similar cut-off points. Melbye et al found that the FEV1/FEV6 ratio that best corresponds to an FEV1/FVC ratio of 70% is 73% with an excellent agreement between these values (5). According to the results of Vandevoorde et al, the FEV1/FEV6 of 73% and FEV6 of 82% are applicable as appropriate alternatives to the FEV1/FVC of 70% and FVC of 80%, respectively (6). They studied patients who referred to medical centers, whereas Melbye et al evaluated a Norwegian population. In the PLATINO study, to compare FEV1/FEV6 with FEV1/FVC, Rosa et al investigated patients aged ≥ 40 years in Sao Paulo and reported FEV1/FEV6 as an appropriate alternative for

FEV1/FVC to detect obstructive lung diseases. Based on an FEV1/FVC of less than 0.7, the best cut-off point of 75% was determined for FEV1/FEV6 with a fixed cut-off of 0.75 for normal adults (17). It is controversial to use a constant threshold < 0.70 for FEV1/FVC or the LLN obtained from population-based normative results adjusted for age, gender, and ethnicity (18). According to the report of Perez-Padilla et al, a decrease in FEV1/FVC and FEV1/FEV6 ratios due to age can lead to an unreal elevation in the diagnosis of obstructive lung disease (19). Van Dijk et

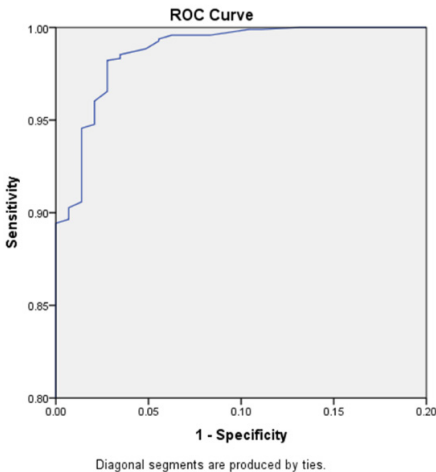


Figure 1. The ROC Curve Achieved for FEV1/FEV6 Taking FEV1/FVC < 70% as the Reference to Detect Obstructive Pulmonary Disease. Note. ROC curve: Receiver operating characteristic curve; FEV1/FEV6: Forced expiratory volume in 1/6 seconds; FVC: Forced vital capacity.

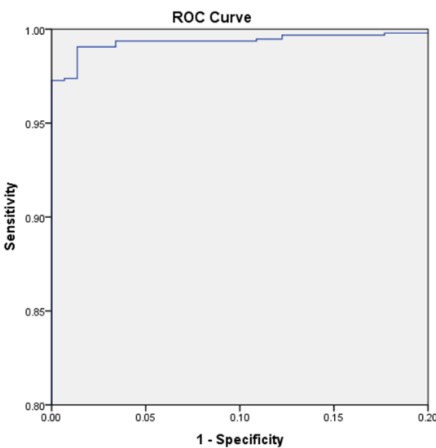


Figure 2. The ROC Curve Achieved for FEV6 Taking FVC < 80% as the Reference to Detect Restrictive Pulmonary Disease. Note. ROC curve: Receiver operating characteristic curve; FEV1/FEV6: Forced expiratory volume in 1/6 seconds; FVC: Forced vital capacity.

al represented an airflow limitation rate of 17% and 11% using a fixed ratio and the LLN, respectively (20). Patients were categorized into those with airflow limitation using a fixed ratio that only had commonly small, non-significant elevations in the probability of adverse outcomes and those with airflow limitation in accordance with the fixed ratio and lower LLN, showing a higher increase in odds. However, the most apparent correlation was observed in patients with airflow limitations by a fixed ratio and LLN, as well as a low FEV1, which was lower than the estimated value of 80% (20). Middle-aged patients are better suited for the determination of cut-off points. Finally, despite the method used for determining the disease, the calculated values similar to the threshold should be cautiously interpreted due to the following factors:

1. Spirometric parameters can change within 24 hours (21).
2. Repeatability of two maneuvers can recognize a difference of 150 cc between the highest amounts of FEV1/FVC as satisfactory (22).
3. The alterations in FEV1 and FVC coefficients in cases with the obstructive disease have shown nearly twice that of normal cases (23).

In a systematic review of studies with no language limit, Jing et al achieved a sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 0.89, 0.98, 45.46, and 0.11 for FEV1/FVC in the diagnosis of airway obstruction, respectively (24). Malolan et al found a significant linear correlation between FVC and FEV6 in their studies. The sensitivity and specificity of FEV1/FEV6 were 100% (25). In the study by Singh and Lohia, 467 spirometries were analyzed when they met the ATS standards. Taking FEV1/FVC < 0.7 as a gold standard for obstruction, a ROC curve was applied for determining the best relevant cut-off of FEV1/FEV6, and the FEV1/FEV6 cut-off of 73% was obtained with the highest sensitivity and specificity. The FEV1/FEV6 sensitivity, specificity, PPV, and NPV were 95.7 %, 94.2%, 87.5%, and 97.9%, respectively (26). The corresponding ratios were 97.22%, 98.22%, 89.17%, and 99.57% in our study, respectively. Aghili et al reported that the common cut-off points for detecting obstruction and restriction are replaceable by FEV1/FEV6 of less than 71% and FEV6 of less than 83%, respectively. FEV1/FEV6 < 71% represented 95.5% sensitivity, 99.4% specificity, 99.3% PPV, and 96.3% NPV. The obstruction rate was also 49.4%. For the restrictive pattern, FEV6 indicated a sensitivity, specificity, PPV, and NPV of 93%, 79.5%, 18%, and 99.5% (restriction rate: 6.3%), respectively (3). Pérez-Padilla et al concluded that the bronchodilator test decreased the overall rate of FEV1/FVC < 0.7 from 21.7% to 14%, suggesting an increased specificity for the detection of COPD. They measured the bronchodilator response regarding FEV1, FVC, FEV1/FVC, and FEV1/FEV6. Expiratory time can change following bronchodilator use, and a comparison between FEV1/FVC prior to and following bronchodilator is

questionable. However, the alteration of FEV1/FEV6 due to bronchodilator use is predictable because it is measured at fixed times, implying that the FEV1/FEV6 ratio is a more reliable index in comparison with the FEV1/FVC ratio (27). Mehrparvar et al also found an association between the FVC in response to bronchodilator and forced expiratory time (FET); however, it was undetectable for FEV6 and FEV3. This indicates that FEV6 is also as an alternative for FVC to assess the bronchodilator response with no need for FET adjustment (28).

In the current study, the cut-off point of FEV6 for the detection of airway restriction was 83%, which can be used as an alternative for FVC < 80%. Restrictive lung disease is linked to a decrease in total lung capacity (TLC), whereas decreased FVC with normal FEV1/FVC represents the probability rather than the diagnosis of restrictive disorders (23). According to Swanney et al, spirometry algorithms could not precisely estimate TLC; however, they are commonly used to detect restrictive diseases. Additionally, utilizing the determined LLN in the NHANES III study, FEV6 was equivalent to FVC (29). Vandevoorde et al studied the restrictive lung disease prevalence (14.9%) and revealed an NPV of 99.3%, which can be considered for detecting restrictive lung disease by FEV6. Nonetheless, the acquired data should be closely assessed, leading to an improvement in the detection of restrictive patterns in older patients (7). We found a prevalence of 13.45% for restrictive lung disease. Using the FEV1/FEV6 ratio, Komal et al evaluated patients suffering from two or more chronic medical conditions hospitalized for the decompensation of chronic disorders. Based on their results, it is impossible to conduct acceptable spirometry during hospitalization in older patients with multimorbidity, which is associated with functional and cognitive impairments. Determining FEV1/FEV6 by a COPD-6 portable device can facilitate spirometric measurements in patients with such limitations (30). Rodríguez-Aguilar et al surveyed disagreements and problems in the diagnosis of chronic obstructive lung disease and demonstrated that the FEV1/FEV6 ratio is more valid compared with the FEV1/FVC, particularly while comparing groups with various expiratory times. In addition to borderline tests, observation over time, and the repeatability of the test are required in this regard (31).

The major strength of the current study was its large sample size, which makes the results generalizable. Our study was not without limitations. One limitation was that a large number of participants made it impossible to perform spirometry in one session. Therefore, spirometry was performed when each patient attended the clinic by different technicians, which might have caused variability in the quality of the performed tests.

Conclusion

Overall, our results indicated FEV1/FEV6 as an accepted surrogate for FEV1/FVC to diagnose airway obstruction,

particularly to screen high-risk patients for COPD. Moreover, FEV6 is potentially an appropriate substitute for FVC to detect restrictive lung diseases.

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Authors' Contribution

AD, HES, and KA designed the study, wrote the manuscript, and analyzed the data, respectively. In addition, FS interpreted the analysis, and GZ revised and polished the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The authors declare that they have no competing interests.

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Ethical Approval

This study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences under the ethics code: IR.HUMS.REC.1397.200. Written informed consent was obtained from all participants.

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