The Concave Shape of the Forced Expiratory Flow-Volume Curve in 3 Seconds Is a Practical Surrogate of FEV_1/FVC for the Diagnosis of Airway Limitation in Inadequate Spirometry

Hao Li MM, Chunhong Liu RN, Yi Zhang MD, and Wei Xiao MD

BACKGROUND: Spirometry is important for the differential diagnosis of dyspnea. However, some patients cannot exhale for ≥6 s to achieve the American Thoracic Society/European Respiratory Society criteria. The aim of this study was to demonstrate the reliability of a new parameter that quantifies the degree of concavity in the first 3 s to define airway limitation as a surrogate for the FEV_1/FVC. METHODS: Four hundred spirometry test results were selected through complete random sampling. The new parameter, termed the AUC_3/AT_3, was calculated as the area under the descending limb of the expiratory flow-volume curve before the end of the first 3 s (AUC_3) divided by the area of the triangle before the end of the first 3 s (AT_3). The AUC_3/AT_3 was compared with the FEV_1/FVC using Pearson's correlation analysis. The level of agreement between the AUC_3/AT_3 and the FEV_1/FVC in the detection of airway obstruction was analyzed using the kappa statistic. We also compared the diagnostic accuracy of the new index with that of the FEV_1/forced expiratory volume in the first 3 s (FEV_3). RESULTS: There was a strong correlation ($r = 0.88$, $P < .001$) between the AUC_3/AT_3 and the FEV_1/FVC. There was also strong agreement between the AUC_3/AT_3 and the FEV_1/FVC in the detection of obstruction with kappa indices of 0.72 (Global Initiative for Chronic Obstructive Lung Disease [GOLD] criterion) and 0.67 (lower limit of normal criterion), and these values were greater than those obtained for the FEV_1/FEV_3. The AUC_3/AT_3 also exhibited acceptable sensitivity, specificity, positive predictive value, and negative predictive value. The diagnostic accuracies of the AUC_3/AT_3 were 86.3% (GOLD criterion) and 83.8% (lower limit of normal criterion), which were greater than the 76.0 and 74.0% obtained for the FEV_1/FEV_3, respectively. CONCLUSIONS: The AUC_3/AT_3 can be utilized as a surrogate parameter for the FEV_1/FVC when patients cannot complete a 6-s expiratory effort. Additionally, the performance of this index is better than that of the FEV_1/FEV_3 in the identification of airway limitations. *Key words: respiratory function tests; spirometry; airway obstruction; maximal expiratory flow-volume curves; area under the curve; diagnosis.* [Respir Care 2017;62(3):363–369. © 2017 Daedalus Enterprises]

Introduction

Lung function tests are important for the differential diagnosis of dyspnea, and FEV_1/FVC is an important index for identifying airway limitation. A reduced FEV_1/FVC without a decreased total lung capacity indicates an obstructive ventilatory defect, and this pattern is typically observed in patients with COPD or asthma.[1] However, complete forced expiration may require a relatively long time in patients with severe airway limitation. Specifically, some elderly patients and patients with severe cough and/or mild cognitive impairment cannot exhale for ≥6 s to achieve the American Thoracic Society/European Respiratory Society criteria.[2] Eaton et al[3] demonstrated that only 28% of subjects could exhale for ≥6 s and that 47% could exhale for <4 s among 2,928 evaluated expiratory efforts. Allen et al[4] demonstrated that 25% of 267 elderly subjects could reach forced expiratory volume in the first 3 seconds (FEV_3) but not FVC.

The authors are affiliated with the Department of Respiratory Medicine, Qilu Hospital, Shandong University, Jinan, Shandong, China.

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Correspondence: Wei Xiao MD, Department of Respiratory Medicine, Qilu Hospital, Shandong University, No. 107, Wenhua Xi Road, Jinan, Shandong 250012, China. E-mail: xiaowei4226@163.com.

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Sometimes, FVC maneuvers are correctly established, and the patients can blow longer than 3 s but cannot satisfy the end-of-test criteria (≥6 s in duration or a plateau in the volume-time curve) after attempting the analysis several times. The FEV_3 has been proposed as an approximate surrogate for the FVC,[4-6] but its reliability remains controversial.[7,8]

The concave shape of the maximal expiratory flow-volume curve reflects slowing expiratory flow,[1] and the curvatures of maximal expiratory flow-volume curves are correlated with symptoms.[9] Because the concavity is mostly observed during the initial time period of the maximal expiratory flow-volume curve, we sought to demonstrate the reliability of the concave shape of the maximal expiratory flow-volume curve in the first 3 s as a practical surrogate for the FEV_1/FVC for the diagnosis of airway limitation in patients who cannot complete a long exhalation.

The area under the maximal expiratory flow-volume curve has been used to describe this concave shape and has been shown to correlate well with the FEV_1. Moreover, this measure is more suitable for the evaluation of bronchial hyper-reactivity and bronchodilation than the FEV_1.[10-12] Furthermore, the area of obstruction is a promising parameter that is well correlated with the exercise capacity of patients with COPD.[13] In this study, the area under the maximal expiratory flow-volume curve in the first 3 s was used to constitute a new parameter to describe the concave shape of the maximal expiratory flow-volume curve in the first 3 s.

QUICK LOOK

Current knowledge

Spirometry tests are important in the management of respiratory diseases. However, some elderly patients and patients with severe airway limitation, cough, or mild cognitive impairment cannot exhale for ≥6 s to achieve the American Thoracic Society/European Respiratory Society criteria. For those subjects who can reach the forced expiratory volume in the first 3 s (FEV_3) but not ≥6 s, the FEV_3 has been investigated as an approximate surrogate for the FVC, although its reliability remains controversial.

What this paper contributes to our knowledge

A new parameter describing the concave shape of the maximal expiratory flow-volume curve in the first 3 s exhibited a strong correlation with the FEV_1/FVC. There was also strong agreement between this new parameter and the FEV_1/FVC in the detection of obstruction based on the fixed ratio and the lower limit of normal. The 3-s index may therefore be used as a surrogate parameter for the FEV_1/FVC when patients cannot complete a 6-s expiratory effort. The performance of this index was also better than that of the FEV_1/FEV_3.

Methods

Calculation of the New Parameter

All original data were obtained from the database of the JLab 4.67 software (CareFusion, Hoechberg, Germany) with the installed JAEGER MasterScreen PFT measuring system (CareFusion, Hoechberg, Germany) of Qilu Hospital of Shandong University. The FEV_1, FEV_3, FVC, and peak expiratory flow values were directly obtained from JLab. Quantitative values of the maximal expiratory flow-volume curves on the x and y axes were obtained from JLab via the graphic output followed by file output. Two pairs of values on the x and y axes were determined as anchoring points. The first point was the peak expiratory flow, and the second was the FEV_3. The area of the right triangle in which the 2 points were vertexes of the hypotenuse was calculated (Fig. 1). We termed this value AT_3 (ie, the area of the triangle before the end of the first 3 s). The curve between the 2 points was plotted with OriginPro 8.0 software (OriginLab, Northampton, Massachusetts), and then the area under this curve and in the right triangle was calculated with the integration command of OriginPro. We termed this value the AUC_3 (ie, the area under the descending limb of the maximal expiratory flow-volume curve before the end of the first 3 s). The new parameter AUC_3/AT_3 was used to describe the degree of concavity of the maximal expiratory flow-volume curve in the first 3 s.

Study Subjects and Procedures

The spirometry results of 400 subjects were randomly selected from the database of the JLab software from January 2016 to March 2016. We also randomly selected 100 healthy subjects without histories of smoking or respiratory symptoms from the health examination population. All spirometry test results were collected with the same type of spirometer. All selected results were acceptable according to the American Thoracic Society/European Respiratory Society task force guidelines.[2] All participants exhibited good starts (extrapolated volume <5% of the FVC or 0.15 L, whichever was greater) and satisfactory exhalation (a plateau in the volume-time curve or ≥6 s), and all participants met the between-maneuver repeatability criteria. Other exclusion criteria were an exhalation time of <3 s, an age >95 y, and no mention of race. The FVC and FEV_1 of each subject were obtained from the curve with the largest sum of the FVC and FEV_1. The

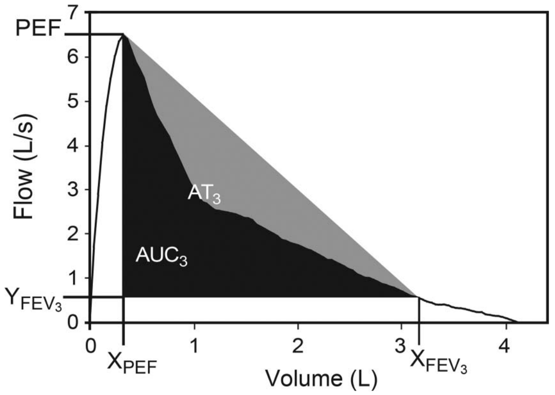

Fig. 1. Graphic explanation of the new parameter (AUC_3/AT_3). X_{PEF} indicates the expired lung volume at the peak expiratory flow. Y_{FEV3} indicates the expiratory flow at the point at which the forced expiratory volume in the first 3 s has been expired. AUC_3 was defined as the area under the descending limb of the expiratory flow-volume curve before the end of the first 3 s and in the right triangle (gray).

AUC_3/AT_3 was calculated from the same curve and compared with the FEV_1/FVC to assess the clinical value of the AUC_3/AT_3 for the diagnosis of airway limitation. As a retrospective study, only medical data from involved patients without any identifying information were used, and the protocol was approved by the ethics committee of Qilu Hospital of Shandong University (Jinan, China).

First, we calculated the correlation between AUC_3/AT_3 and FEV_1/FVC. We then tested the new parameter against air flow limitation. Currently, there are 2 different spirometric criteria for defining airway obstruction. One criterion is a simple fixed cutoff point of the FEV_1/FVC, such as the 0.70 recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) consortium (Global Strategy for the Diagnosis, Management and Prevention of COPD. GOLD 2016, http://goldcopd.org/). The other criterion is based on the lower limit of normal values for FEV_1/FVC recommended by the American Thoracic Society, European Respiratory Society, and Global Lung Function Initiative.[14] Thus far, no evidence has demonstrated the superiority of either criterion in the diagnosis of obstructive airway diseases such as COPD.[15,16] Therefore, we assessed the new index using both of these criteria. We also compared the diagnostic accuracy of the new index with that of FEV_1/FEV_3.

The predicted values of FEV_1 and FEV_1/FVC were calculated based on age, sex, height, and ethnicity. Height was measured without shoes to the nearest centimeter. The GLI-2012 prediction equations for northeastern Asian subjects and the Excel sheet calculator (http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/excel-sheet-calculator.aspx, *Accessed April 2, 2016*) were used in this study. The lower limit of normal was defined at the 5th centile (Z score: −1.64). The new index and the FEV_1/FEV_3 were compared with the lower limit of normal of the FEV_1/FVC from the GLI-2012 reference set when using the lower limit of normal criterion.

Statistical Analysis

We chose to recommend the new parameter as an alternative if we observed a 95% certainty (ie, a probability of type-2 error of 0.05) and a sensitivity and specificity that were not ≥0.80. We calculated the sample size using the formula in the publication of Arkin and Wachtel.[17]

The correlation between the 2 parameters was determined using a 2-tailed Pearson's correlation analysis. A kappa test was used to assess the agreements between the AUC_3/AT_3 and FEV_1/FVC and between the FEV_1/FEV_3 and FEV_1/FVC in terms of the identification of airway obstruction as defined by the GOLD or lower limit of normal criterion. The diagnostic performance of the index was evaluated based on the specificity, sensitivity, negative predictive value, positive predictive value, and diagnostic accuracy.

The statistical analyses were performed with SPSS 22 (IBM, Armonk, New York). All tests were performed at a significance level of $P < .05$.

Results

In total, 400 study subjects (37.3% female) and 100 healthy subjects (45% female) were included in this study. The ages of the study subjects ranged from 16.1 to 85.2 y, and the mean ± SD age was 52.3 ± 13.5 y. Table 1 provides the descriptive statistics for the spirometric parameters. No subject completed FVC before the end of 3 s. A total of 245 subjects (61.3%) exhibited airway obstruction (lower limit of normal criterion).

The scatter diagrams in Figure 2 illustrate the correlation of AUC_3/AT_3 and FEV_1/FVC as well as that of FEV_1/FEV_3 and FEV_1/FVC. There was a strong correlation ($r = 0.88$, $P < .001$) between AUC_3/AT_3 and FEV_1/FVC. There was also a strong correlation ($r = 0.95$, $P < .001$) between FEV_1/FEV_3 and FEV_1/FVC.

The linear regression equations of AUC_3/AT_3 and FEV_1/FEV_3 were: $AUC_3/AT_3 = 1.086 \times FEV_1/FVC - 0.031$ (the residual SD was 0.080) and $FEV_1/FEV_3 = 0.643 \times FEV_1/FVC + 0.321$ (the residual SD was 0.032).

There was strong agreement between AUC_3/AT_3 and FEV_1/FVC, with kappa indices of 0.72 (GOLD criterion) and 0.67 (lower limit of normal criterion), which were higher than the 0.54 and 0.51 obtained for FEV_1/FEV_3, respectively (Table 2). The sensitivities of AUC_3/AT_3 were 86.5% (GOLD criterion) and 82.4% (lower limit of normal criterion), which were higher than the 58.3 and 57.6% obtained for FEV_1/FEV_3, respectively. However, the specificities of AUC_3/AT_3 were 85.9% (GOLD criterion) and

Table 1. Demographic Data and Conventional Spirometric Values of the Subjects

	Study group (n = 400)		Healthy Group (n = 100)	
	Mean ± SD	Range	Mean ± SD	Range
Male (n)	251		55	
Age, y	52.3 ± 13.5	16.1 to 85.2	54.5 ± 12.7	19.5 to 75.7
Height (cm)	166.2 ± 7.5	140 to 185	161.4 ± 7.7	146 to 176
Weight (kg)	68.9 ± 11.8	40.0 to 105.5	66.1 ± 10.3	42.0 to 86.0
BMI, kg/m^2	25.5 ± 3.9	15.0 to 42.2	25.4 ± 3.6	17.9 to 32.5
FEV_1 (L)	1.68 ± 0.71	0.48 to 3.80	2.63 ± 0.70	1.46 to 4.57
FEV_1%pred	69.5 ± 31.6	16.8 to 145.0	96.3 ± 13.5	64.1 to 133.8
FEV_1 (z-score)	–2.84 ± 2.63	–7.80 to 3.42	–0.27 ± 1.16	–2.98 to 3.31
FEV_1/FVC	0.65 ± 0.15	0.25 to 0.9	0.79 ± 0.04	0.72 to 0.89
FEV_1/FVC (z-score)	–2.5 ± 1.95	–6.81 to 1.22	–0.29 ± 0.77	–2.02 to 1.13
FEV_1/FEV_3	0.74 ± 0.10	0.47 to 0.94	0.83 ± 0.03	0.74 to 0.90
AUC_3/AT_3	0.68 ± 0.18	0.22 to 1.23	0.84 ± 0.12	0.62 to 1.18

BMI = body mass index
pred = predicted value
FEV_3 = forced expiratory volume in 3 second
AUC_3 = the area under the descending limb of expiratory flow-volume curve before the end of the first 3 seconds
AT_3 = the area of triangle before the end of the first 3 seconds

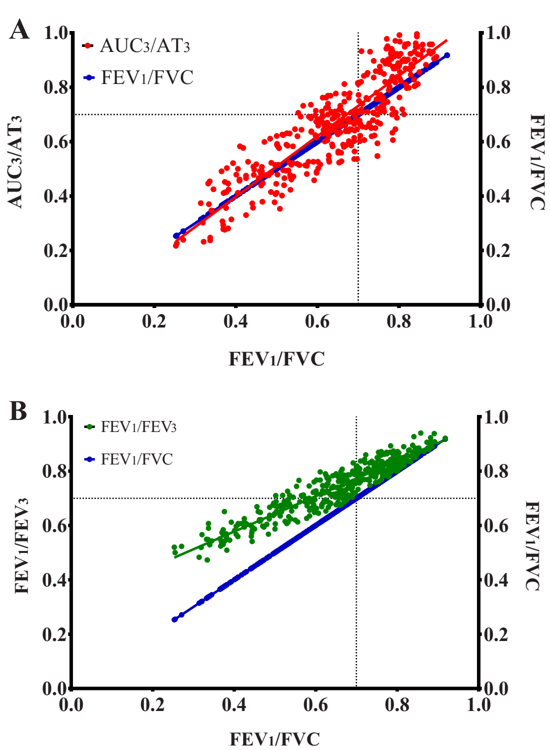

Fig. 2. Scatter diagrams illustrating the correlations between the AUC_3/AT_3 and FEV_1/FVC (A) and between the FEV_1/FEV_3 and FEV_1/FVC (B).

85.8% (lower limit of normal criterion), which were lower than the 100% obtained for FEV_1/FEV_3 according to each criterion. The positive predictive values and negative predictive values of the AUC_3/AT_3 and FEV_1/FEV_3 are provided in Table 3. The diagnostic accuracies of the AUC_3/AT_3 were 86.3% (GOLD criterion) and 83.8% (lower limit of normal criterion), which were higher than the 76.0 and 74.0% obtained for the FEV_1/FEV_3, respectively (Table 3).

Discussion

Spirometry tests are important in the management of respiratory diseases. Obstructive ventilatory impairment is defined by a reduced FEV_1/FVC. However, completing an acceptable spirometry assessment in accordance with the standards set by the American Thoracic Society/European Respiratory Society may be difficult for some patients. When the patient cannot complete an adequate forced expiration, the application form is returned to the doctor without any acceptable result.

However, it is well known that the concave shape toward the volume axis of the maximal expiratory flow-volume curve correlates with air-flow obstruction. In the early stage of COPD, this curve changes even without alterations in FEV_1 or FEV_1/FVC.[1] As the obstructive disease worsens, the concave shape becomes more obvious. Thus, the maximal expiratory flow-volume curve contains much information that can be used to diagnose airway limitation. However, it remains difficult to quantify the degree of concavity and to confirm the correlation with the current classical spirometry parameters. Some new parameters describing the concave shape have been put forward, such as the "angle beta,"[18,19] "slope ratio,"[20-22] and the "area under the maximal expiratory flow-volume curve."[10-12,23-26]

Table 2. The Agreements Between the AUC_3/AT_3 and FEV_1/FVC and Between the FEV_1/FEV_3 and FEV_1/FVC for the Identification of Airway Obstruction as Defined by the Gold and LLN Criteria (Kappa Tests)

	GOLD Criterion		LLN Criterion		Kappa	*P*
	$FEV_1/FVC < 0.70$	$FEV_1/FVC \geq 0.70$	$FEV_1/FVC <$ LLN	$FEV_1/FVC \geq$ LLN		
$AUC_3/AT_3 < 0.70$	199	24			0.72	<.001
$AUC_3/AT_3 \geq 0.70$	31	146				
$AUC_3/AT_3 <$ LLN			202	22	0.67	<.001
$AUC_3/AT_3 \geq$ LLN			43	133		
$FEV_1/FEV3_3 < 0.70$	134	0			0.54	<.001
$FEV_1/FEV3_3 \geq 0.70$	96	170				
$FEV_1/FEV3_3 <$ LLN			141	0	0.51	<0.001
$FEV_1/FEV3_3 \geq$ LLN			104	155		

FEV_3 = forced expiratory volume in 3 second
AUC_3 = the area under the descending limb of expiratory flow-volume curve before the end of the first 3 seconds
AT_3 = the area of triangle before the end of the first 3 seconds
GOLD = Global initiative for Chronic Obstructive Lung Disease
LLN = lower limit of normal

Table 3. Sensitivity, Specificity, PPV, NPV and Diagnostic Accuracy of the AUC_3/at_3 for the Diagnosis of Airway Obstruction Based on the Two Criteria

	Sensitivity	Specificity	PPV	NPV	DA
GOLD criterion					
AUC_3/AT_3	86.5%	85.9%	89.2%	82.5%	86.3%
FEV_1/FEV_3	58.3%	100%	100%	63.9%	76.0%
LLN criterion					
AUC_3/AT_3	82.4%	85.8%	90.2%	75.6%	83.8%
FEV_1/FEV_3	57.6%	100%	100%	52.1%	74.0%

PPV = positive predictive values
NPV = negative predictive values
DA = diagnostic accuracy
AUC_3 = the area under the descending limb of expiratory flow-volume curve before the end of the first 3 seconds
AT_3 = the area of triangle before the end of the first 3 seconds
LLN = lower limit of normal
GOLD = Global initiative for Chronic Obstructive Lung Disease

The purpose of this study was to identify a method to discriminate airway obstruction from normal expiration in subjects with an incomplete spirometry of >3 s but <6 s. The above parameters require complete exhalation, so we constructed a new parameter that is independent of FVC to describe the maximal expiratory flow-volume curve pattern. Our study results demonstrate that this new AUC_3/AT_3 parameter is strongly correlated with the FEV_1/FVC, and the difference between the 2 indices is minimal, as demonstrated in the scatter diagram (Fig. 2A). Our study further demonstrated strong agreement between the AUC_3/AT_3 and FEV_1/FVC in the detection of airway obstruction based on the fixed ratio or the lower limit of normal. Thus, the AUC_3/AT_3 offers a good practical value for patients who cannot complete a full expiration.

However, this surrogate parameter should be applied appropriately. The FEV_1/FVC remains the accepted standard criterion for defining airway limitation, and we should encourage patients to achieve satisfactory spirometry FVC maneuvers (we should even ask patients to return for second measurements when full exhalation may be possible). Technician training can also contribute to the quality of spirometry.[3] The major merit of the new 3-s index is its reasonable accuracy in interpreting incomplete spirometry results from subjects who cannot blow for ≥6 s after their best attempts. Among the 100 healthy subjects, none had an FEV_1/FVC <0.70, but there were 2 subjects with FEV_1/FVC values below the lower limit of normal. The diagnostic accuracies were 100% (GOLD criterion) and 98% (lower limit of normal criterion) between the FEV_1/FEV_3 and FEV_1/FVC and 96% (GOLD criterion) and 95% (lower limit of normal criterion) between the AUC_3/AT_3 and FEV_1/FVC. In our study, there were 25 subjects who exhibited expirations of <6 s with a valid expiratory plateau. These subjects were primarily young people or subjects with restrictive ventilatory defects. The FEV_1/FVC values of these 25 subjects were much greater than 0.70 or their own lower limits of normal. The diagnostic accuracy was 100% between the FEV_1/FEV_3 and FEV_1/FVC, but this value was 96% between the AUC_3/AT_3 and FEV_1/FVC according to the GOLD criterion. Thus, this new parameter exhibited no advantage over the FEV_1/FEV_3 among healthy subjects and the subjects whose expirations were objectively <6 s.

There were 215 subjects with FEV_1/FVC values that ranged between 0.60 and 0.80. In this group, the sensitivity and specificity of the AUC_3/AT_3 were 74.5 and 78.0%, respectively, according to the GOLD criterion. It is common for sensitivity or specificity of any diagnostic index to be low when it is assessed separately for the area near the cutoff point for any diagnostic index. The results near the cutoff point require careful interpretation by practitioners.

Additionally, the completeness of expiration is difficult to judge in some situations. The expiratory flows of some patients with severe airway obstruction are so slow that the FVC is likely to be under-recorded.[1] A lower than anticipated FVC leads to a larger FEV_1/FVC, which may represent a false negative. Townsend et al[7] demonstrated that subjects with severe obstructions are misclassified even after 6 s of expiration. For the 4 subjects with low FEV_1/FVC values (0.504 ± 0.058), the mean FEV_1/FVC values were overestimated as 0.693 (after 3 s), 0.590 (after 6 s) and 0.541 (after 10 s).[7] The AUC_3/AT_3 also can be used as a reference index to detect an incomplete exhalation. When the FEV_1/FVC is significantly greater than the AUC_3/AT_3, the slow vital capacity or total lung volume should be measured. Currently, the FEV_3 and the expiratory flow-volume area can be recorded with many spirometers. Therefore, the AUC_3/AT_3 can also be calculated automatically and reported with the help of the manufacturers of spirometers. Thus, we encourage these manufacturers to include the option of reporting the AUC_3/AT_3, and we encourage the analysis of existing spirometry databases to establish normal values and lower limits of normal for the AUC_3/AT_3.

Although the correlation between the FEV_1/FEV_3 and FEV_1/FVC was very strong, this finding resulted from the derivation of the 2 indices from the same data. The FEV_3 is inevitably less than or equal to the FVC, and it differs more in subjects with severe obstructive air-flow limitation (Fig. 2B). Townsend et al[7] demonstrated that the FEV_1/FVC is overestimated when using the FEV_3 instead of the FVC, and this deviation increases with the severity of obstruction. Mehrparvar et al[8] also demonstrated the low sensitivity of the FEV_1/FEV_3 when used as a surrogate for the FEV_1/FVC in the diagnosis of airway obstruction. We reached the same conclusion in the present study. However, the FEV_1/FEV_3 could serve as an exclusion index due to its high specificity.

The present study has some limitations. First, the proportion of subjects with airway obstruction in our study was obviously greater than that in the general population because our population comprised people who visited the hospital with dyspnea. Therefore, the negative predictive value was lower and the positive predictive value was higher than the values in the general population. These differences should be considered if the AUC_3/AT_3 is to be used as a screening index. Second, some subjects who could complete expiration also exhibited incomplete inhalations, and the influence of these cases on the AUC_3/AT_3 was not investigated in this study. Thus, subgroup analysis is required in further studies. Third, the index defined by 3 s seems to be more repeatable in subjects than the FEV_1/FVC because it provides a more explicit end, and the test becomes less physically demanding. However, the within-subject repeatability for the new index requires further prospective study.

Conclusions

The AUC_3/AT_3 can be utilized as a surrogate parameter for the FEV_1/FVC when patients cannot complete a 6-s expiratory effort. This index is more effective than the FEV_1/FEV_3 in the identification of airway limitation.

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