ORIGINAL RESEARCH

Factors for the Variability of Three Acceptable Maximal Expiratory Flow–Volume Curves in Chronic Obstructive Pulmonary Disease

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Background: Generally, the maximal expiratory flow–volume (MEFV) curve must be measured for the diagnosis and staging of chronic obstructive pulmonary disease (COPD). As this test is effort dependent, international guidelines recommend that three acceptable trials are required for each test. However, no study has examined the magnitude and factors for the variability in parameters among three acceptable trials.

Methods: We evaluated the intra-individual variations in several parameters among three acceptable MEFV curves obtained at one-time point in patients with COPD (n = 28, stage 1; n = 36, stage 2; n = 21, stages 3–4). Next, the factors for such variations were examined using forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC).

Results: The averages of coefficient of variation (CV) for FEV_1 and FVC were 2.0% (range: 1.0–3.0%) and 1.6% (0.9–2.2%), respectively. Both parameters were significantly better than peak expiratory flow rate, forced expiratory flow at 50% of expired FVC, and forced expiratory flow at 75% of expired FVC (CVs: 5.0–6.9%). A higher spirometric stage was significantly associated with higher CVs for FVC and FEV_1, and older age was significantly correlated with a higher variation in FEV_1 alone. Furthermore, a significantly inverse association was observed between emphysema severity, and the CVs for FEV_1, but not that for FVC, regardless of spirometric stage.

Conclusion: Both FVC and FEV_1 are highly reproducible; nevertheless, older age, lower FEV_1 at baseline, and non-emphysema phenotype are factors for a higher variability in FEV_1 in patients with COPD.

Keywords: chronic obstructive pulmonary disease, coefficient of variation, flow–volume curve, forced expiratory volume in 1 second, variability

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is not completely reversible.[1,2] Generally, the assessment of airflow limitation is based on spirometric testing with maximal expiratory flow–volume (MEFV) curve. Forced expiratory volume in 1 second (FEV_1), forced expiratory volume (FVC), and FEV_1/FVC, all of which are derived from the MEFV curve, are the most important variables in the diagnosis and staging of COPD. However, the test has some inherent challenges. That is, it requires cooperation and maximal effort from participants. The American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force (TF)[3] and the Japanese Respiratory Society (JRS)[4] established the guidelines on spirometry. These

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recommendations show that to appropriately collect data, at least three acceptable MEFV trials are required for each test.

Several classical studies[5–13] have evaluated between-day variability, within-day variability, and serial-measurement variability in parameters derived from MEFV curves in patients with COPD and healthy participants. There is a consensus that forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) are highly reproducible within an acceptable range. However, to the best of our knowledge, no study has examined the magnitude of variability and the factors for such variability in these parameters among three acceptable MEFV curves in patients with COPD. We believe that this study can provide important information that can be used when interpreting spirometric data, particularly when assessing longitudinal changes and/or the effects of pharmacological intervention on pulmonary function.

Materials and Methods

Participants

The spirometric data of patients with COPD were obtained from the Hokkaido COPD cohort study, which has been described in detail in our previous studies.[14,15] The diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Importantly, we excluded participants with asthma, which was diagnosed clinically by respiratory physicians.

Of 300 participants with COPD who were initially recruited for the original cohort, we attempted to analyze 143 who underwent pulmonary function tests (PFTs) at Hokkaido University Hospital to prevent any influence on the variability of MEFV curve due to the different quality of the machines used and/or the different skills of technicians in other hospitals. In the original cohort, participants with clinically stable condition underwent PFTs at 6-month intervals. In this study, we used data collected on visit 7 from 2006 to 2008 because three acceptable MEFV curves were obtained. This was based on the official announcement regarding the recommended spirometry by the JRS[4] in 2004 and the ATS/ERS[3] in 2005. Until then, we had not defined the acceptability of the three MEFV curves using a strict method. That is, we did not stick with a time-to-PEF that is <120 ms.[16]

Eventually, 85 participants were assessed in this study. We selected the best curve from three acceptable ones for later analysis. The ethics committee of Hokkaido University School of Medicine approved the whole study protocol (approval number: 02–001), which was in accordance with the amended Declaration of Helsinki.

Symptoms of Chronic Bronchitis

Data on disease history, smoking history and other information were collected by well-trained clinical research coordinators. Chronic cough and sputum expectoration were considered when participants claimed that they present with these symptoms on most days for >3 months/year and for >2 consecutive years. To prevent bias caused by the patients' reports the presence of chronic sputum was defined as a sputum volume >10 mL/day.[17,18] The participants were classified into three groups according to the severity of wheezing within the last 6 months before the examination day: group A: none (n = 52); B: only 2–3 days/month (n = 23); and C: few days/weeks to almost every day (n = 10).

Pulmonary Function Tests

The MEFV curves were obtained using a rolling-seal spirometer (CHESTAC-33; Chest M.I., Inc., Tokyo, Japan). The PFTs were conducted in accordance with the 2004 JRS standards.[4] The accuracy of the spirometer was assessed daily using a 3-liter calibration syringe. Testing was allowed on a given spirometer if the measured volume errors were <3%. Two well-trained technicians performed the PFT. FVC, FEV_1, peak expiratory flow rate (PEF), forced expiratory flow at 50% of expired FVC (FEF_{50}), and forced expiratory flow at 75% of expired FVC (FEF_{75}) were obtained using the MEFV curves. The MEFV curves were considered acceptable if all peak expiratory flow values were within 10% of the maximum observed and if there was a rapid start, absence of major flow fluctuations, and adequate expiration time. Furthermore, the reproducibility was considered acceptable when the differences between the best and the second-best MEFV curve for both FVC and FEV_1 were <200 mL. In brief, three acceptable and two reproducible maneuvers were required in up to 8 forced trials.[4] The predicted values were calculated according to the JRS equations.[19] The diffusing capacity of the lungs for carbon monoxide (DL_{CO}) was also measured using the single-breath method. Moreover, DL_{CO} and Krogh's constant for CO (K_{CO}) (DL_{CO}/alveolar volume [V_A]), both of which were adjusted for hemoglobin levels, were calculated. The percent predicted values were obtained using the Burrows equation.[20] All PFTs were performed between 9 AM and 12 PM to prevent

any circadian variations. To assess reversibility in airflow limitation, the MEFV curves were measured again after the patient inhaled 0.4 mg of salbutamol. Prior to all PFTs, the participants were instructed to withdraw from using short-acting bronchodilators, long-acting β_2 agonists or sustained-release theophylline, and long-acting anticholinergic inhalers within 12, 24, and 48 h, respectively, prior to testing.

Computed Tomography Scan Data Acquisition and Analysis

Computed tomography (CT) scan was performed using a multidetector-row spiral CT scanner with 64 detector arrays (Aquilion Multi, TSX-101A/6A; Toshiba Medical Systems, Gunma, Japan). Data were acquired with the following parameters: 120 kVp; 300 mA; 64 detector × 0.5-mm collimation; slice thickness, 0.5 mm; 0.5 s/rotation; and helical pitch, 41. The whole lung was scanned while the patient was holding his or her breath during deep inspiration while in supine position. On the examination day, the patients were instructed to take their medications as usual. Data were transferred to a workstation and then reconstructed into three-dimensional images. The detailed process of CT scan data acquisition and reconstruction has been described previously.[21] The severity of emphysema was scored according to the percentage of low attenuation volume (%LAV), which was automatically assessed using our original proprietary software.

Blood Samples

To measure eosinophil count and immunoglobulin (Ig) E levels, blood samples were collected from all participants on the same day.

Statistical Analysis

To evaluate the variability of three acceptable MEFV curves, we calculated the coefficient of variations (CVs) for those parameters derived from the MEFV curve. To identify factors that might influence the variability in FVC and FEV_1, we examined the demographic characteristics of the participants (sex, age, BMI, and smoking status), clinical symptoms (chronic cough, chronic sputum, and frequency of wheezing), some PFT parameters (baseline %FEV_1, reversibility of airflow limitation, and %K_{CO}), blood markers (serum total IgE and eosinophil levels), and emphysema score (%LAV). Based on the GOLD

definition, the reversibility of airflow limitation was considered positive when the post-bronchodilator increase in FEV_1 was >200 mL and 12% compared with the baseline. In almost all analyses, we used the pre-bronchodilator data alone as baseline data except when analyzing changes in CVs after inhaling salbutamol.

Data were expressed as mean and standard error when normally distributed and as median and interquartile range (IQR) when skewed. CV data were logistically transformed when considered appropriate. When all three data were equal (CV = 0), a log CV of 0.31 was used for later analysis because it was considered appropriate. The following variables were examined using the Pearson γ for continuous variables, unpaired t-test, or Kruskal–Wallis test for categorical variables.

To evaluate the differences in CV value for FVC or FEV_1 in the strata of COPD stage or age, we used the Kruskal–Wallis test, followed by the Mann–Whitney U-test, for comparison among multiple groups.

A multiple, stepwise analysis was performed to identify the factors that significantly influenced the variability in FEV_1 and FVC. All statistical analyses were two-sided and p values <0.05 were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences software version 22 (SPSS Inc., Chicago, IL).

Results

The characteristics of the participants (n = 85) are shown in Table 1. Figure 1 shows the comparison of CVs for the five parameters derived from the MEFV curves. The median (interquartile range) CVs for FVC and FEV_1 were as 1.6% (range: 0.9–2.2%) and 2.0% (range: 1.0–3.0%). These values were significantly lower than those for PEF, FEF_{50}, and FEF_{75} (5.0% [3.3–6.8], 5.6% [3.9–8.4], and 6.9% [5.1–10.8], p < 0.0001)

Next, we evaluated factors that could influence the variability in FEV_1 and FVC. A univariate analysis showed that old age, presence of wheezing, baseline %FEV_1, and high airway reversibility were significantly associated with higher CVs for FEV_1. Meanwhile, older age and lower %FEV_1 at baseline alone were associated with higher CVs for FVC (Table 2). Based on the effect of age or baseline %FEV_1 according to the categorized data, participants aged over 81 years were found to have a significantly higher variability in FEV_1. Moreover, patients with stage 3 or 4 COPD had a significantly higher variability in both FVC and FEV_1 than those with mild- or
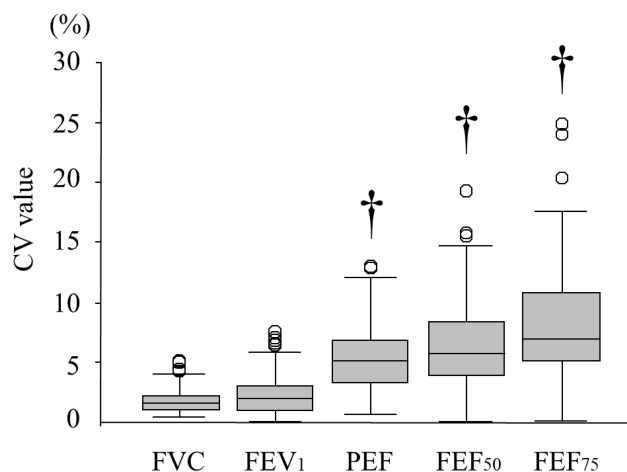
Table 1 Characteristics of the Participants

Characteristics	Overall (n=85)
Age, years	72.4 (8.3)
Gender (male/female)	78/7
BMI (kg/m^2)	22.4 (0.3)
Smoking, pack-years	65.4 (28.5)
Current smoker, N (%)	12 (14.1)
Clinical symptoms	
Chronic cough, N (%)	13 (15.3)
Chronic sputum, N (%)	19 (22.4)
The frequency of wheeze[a] A/B/C, N	52/23/10
Lung function	
Pre-bronchodilator	
FEV$_1$, L	1.42 (1.05–2.04)
FEV$_1$, % predicted	60.0 (43.4–80.8)
FVC, % predicted	107.7 (91.1–119.5)
FEV$_1$/FVC, %	46.5 (36.2–57.3)
K$_{CO}$, % predicted	68.2 (55.0–86.1)
Post-bronchodilator	
FEV$_1$, L	1.61 (1.21–2.18)
FEV$_1$, % predicted	65.3 (51.2–85.7)
FVC, % predicted	113.1 (97.5–126.0)
FEV$_1$/FVC, %	47.8 (37.9–59.8)
Reversibility, N (%)	17 (20.0)
GOLD stage[b] 1/2/3/4, N	28/36/18/3
Blood analysis	
Serum total IgE (log cells/µL)	1.80 (0.07)
Peripheral eosinophils (log cells/µL)	2.22 (0.03)
LAV, % total lung volume	24.3 (14.9–39.4)

Notes: Data with normal distribution were presented as mean (SD), and data with skewed distribution were expressed as median (IQR). Data on the frequency of wheezing[a] were obtained via interview within the last 6 months prior to the examination day: group A: none, B: only 2–3 days/month, and C: few days/weeks to almost every day. GOLD stage[b] 1 was defined as predicted FEV$_1$/FVC ratio <70% and predicted FEV$_1$ >80%. GOLD stage 2 was defined as predicted FEV$_1$/FVC ratio between 70% and 50% and predicted FEV$_1$ ≤ 80%. GOLD stage 3 was defined as predicted FEV$_1$/FVC ratio between 70% and 30% and predicted FEV$_1$ ≤ 50%. GOLD stage 4 was defined as predicted FEV$_1$/FVC ratio <70% and predicted FEV$_1$ ≤ 30% or < 50% plus chronic respiratory failure.
Abbreviations: BMI, body mass index; BD, bronchodilator; FVC, forced expiratory capacity; FEV$_1$, forced expiratory volume in 1 s; K$_{CO}$, Krogh's constant for CO (DL$_{CO}$/V$_A$); DL$_{CO}$, diffusing capacity of the lungs for carbon monoxide; V$_A$, alveolar volume; GOLD, Global Initiative for Chronic Obstructive Lung Disease; Ig, immunoglobulin; LAV, low attenuation volume.

Figure 1 Differences in coefficient of variations (CVs) for the parameters of flow–volume curves in 85 participants with COPD. Based on the three best maneuvers, the median (IRQ) CV for FVC (1.6% [range: 0.9–2.2%] or FEV$_1$ (2.0% [range: 1.0–3.0%], p < 0.0001) were significantly lower than the PEF, FEF$_{50}$, and FEF$_{75}$ (5.0% [range: 3.3–6.8%], p < 0.0001; 5.6% (range: 3.9–8.4%), p < 0.0001; and 6.9% (range: 5.1–10.8), p < 0.0001, respectively). This result indicated that FVC or FEV$_1$ had consistent values in spirometry even in participants with COPD. Data were presented as median (IRQ) (†p < 0.0001).

1.85 ± 0.91 and 1.88 ± 0.91 in the youngest age group whose age below 60 years old. There were no trends of either increase or decrease among three consecutive attempts in participants of the other two age groups (data not shown).

To assess the independent factors for the variability in FVC and FEV$_1$, a stepwise analysis was performed using data on demographic characteristics, clinical symptoms, PFT results, blood marker levels, and emphysema severity. This analysis revealed that older age, lower %FEV$_1$ at baseline, and lower emphysema score were independently correlated with higher CVs for FEV$_1$ (p = 0.008, 0.001, and 0.006, respectively). By contrast, baseline %FEV$_1$ alone was significantly associated with CVs for FVC (p = 0.005) (Table 3).

The minimal clinically important difference (MCID) value for FEV$_1$ in COPD, which is a clinically relevant value in data interpretation, was considered with respect to the data in this study. Hence, the difference between the highest and lowest value among the three acceptable MEFVs in FVC and FEV$_1$ was assessed. The average for the variability in FEV$_1$ was 56.9 ± 35.2mL. Table 4 shows the percentage of participants with a difference >100mL according to spirometric stage, which is the MCID for FEV$_1$.[22]

Discussion

FEV$_1$, FVC, and FEV$_1$/FVC, all of which were derived from the MEFV curve, are vital pulmonary function

moderate-stage disease (Figure 2). We further compared the serial data of means at the first to the third acceptable attempt, using the categorizing data based on age, in an attempt to find a fatigue effect particularly in the elderly and/or a training effect in any age groups. In participants over 81 years old, the mean value (±SD) for FEV$_1$ at first, second and third attempts were 1.12 ± 0.51L, 1.13 ± 0.50 and 1.13 ± 0.47, respectively, while 1.88 ± 0.89L,

Table 2 Relationships Between Variability in FVC or FEV$_1$ (Log CV for FVC or FEV$_1$) as Well as Demographic Characteristics, Clinical Symptoms, PFT Findings, Blood Analysis Results, and CT Scan Variables

Variables	Statistical Test		No	FVC (Log CV, %)			FEV$_1$ (Log CV, %)		
				Mean (SD)	Statistic	p value	Mean (SD)	Statistic	p value
Sex	Unpaired *t*-test	Male	78	0.147 (0.290)		0.681	0.247 (0.351)		0.531
		Female	7	0.099 (0.342)			0.199 (0.342)		
Age	Pearson correlation		85		0.261	0.016		0.381	<0.0001
BMI	Pearson correlation		85		−0.047	0.67		−0.074	0.5
Smoking status	Unpaired *t*-test	Former	72	0.122 (0.298)		0.96	0.232 (0.358)		0.226
		Current	13	0.274 (0.223)			0.308 (0.295)		
Chronic cough	Unpaired *t*-test	+	13	0.247 (0.245)		0.163	0.298 (0.349)		0.673
		-	72	0.124 (0.298)			0.233 (0.351)		
Chronic sputum	Unpaired *t*-test	+	19	0.119 (0.304)		0.162	0.295 (0.353)		0.81
		-	66	0.226 (0.238)			0.228 (0.349)		
Frequency of wheezing[a]	Kruskal–Wallis test	A	52	0.122 (0.287)		0.301	0.167 (0.349)		0.034
		B	23	0.127 (0.322)			0.320 (0.305)		
		C	10	0.289 (0.231)			0.460 (0.346)		
Pre-BD FEV$_1$ (% predicted)	Pearson correlation		85		−0.293	0.007		−0.34	<0.0001
Reversibility	Unpaired *t*-test	+	17	0.165 (0.256)		0.738	0.466 (0.190)		0.004
		-	68	0.137 (0.302)			0.187 (0.358)		
Serum total IgE (log)	Pearson correlation		85		0.169	0.132		−0.084	0.453
Peripheral eosinophils (log)	Pearson correlation		85		0.055	0.618		0.054	0.624
%LAV	Pearson correlation		85		−0.083	0.453		−0.85	0.44

Notes: Data on the frequency of wheezing[a] were obtained via interview within the last 6 months prior to the examination day: group A: none, B: only 2–3 days/month, and C: few days/weeks to almost every day.
**Abbreviations:** CV, coefficient of variation; FVC, forced expiratory capacity; FEV$_1$, forced expiratory volume in 1 s; BMI, body mass index; BD, bronchodilator; Ig, immunoglobulin; LAV, low attenuation volume.

parameters for the diagnosis and staging of COPD. Moreover, they play an important role in the assessment of the natural history of a disease and the efficacy of pharmacotherapy. The MEFV curve is completely dependent on a participant's cooperation and maximal effort. The results obtained via one-time measurement must be cautiously interpreted. Thus, the international guidelines recommend that at least three acceptable trials are required for clinical research settings.

This study showed that the median (interquartile range) of coefficient of variation (CV) for FEV$_1$ and FVC were 2.0% (range: 1.0–3.0%) and 1.6% (range: 0.9–2.2%), respectively. These values were significantly better than PEF, FEF$_{50}$, and FEF$_{75}$ (range: 5.0–6.9%). The COPD spirometric stage was significantly associated with higher

CVs in FVC and FEV$_1$, and older age was significantly correlated with a higher variation in FEV$_1$ alone. Furthermore, a significant inverse association was observed between emphysema severity and the CVs for FEV$_1$, but not that for FVC, regardless of spirometric stage.

One may speculate that age effect on a high variation in FEV$_1$ is due to weaker expiratory muscles, in other words, a fatigue effect. However, we did not notice any significant differences from the first to the third attempt in the three acceptable trials even of the elderly group. As the age effect was significant only on FEV$_1$, but not FVC, it may indicate that the higher variability in FEV$_1$ is due to the instability of airways in older patients with COPD. By comparing serial three attempts as mean data of FEV$_1$ and
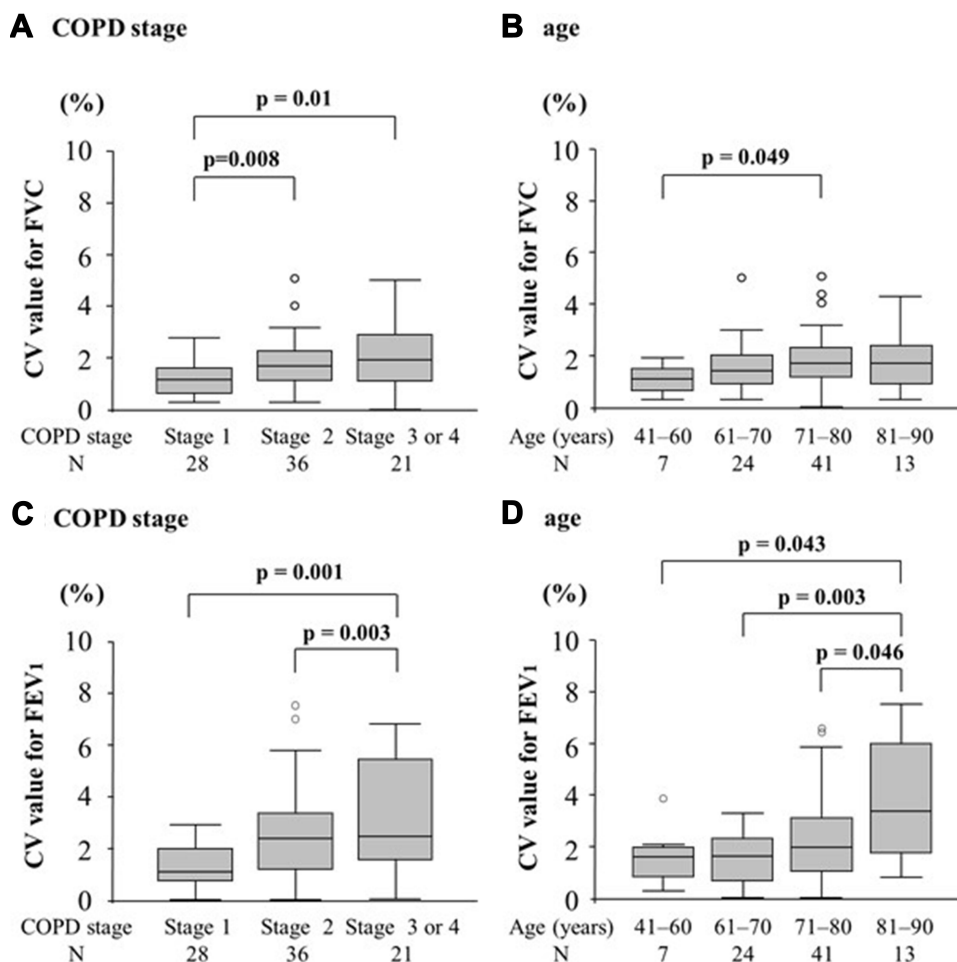
Figure 2 Differences in CVs for FVC or FEV_1 according to COPD stage based on the GOLD criteria and age. (**A**) The median CV for FVC in stage 3 or 4 COPD (1.9% [range: 1.2–2.8%]) significantly varied compared with that in stage 1 COPD (1.2% [range: 0.7–1.6%], p = 0.01). In addition, stage 2 COPD (1.7% [range:1.2–2.3%]) significantly varied compared with stage 1 COPD (p = 0.008). (**B**) The median CV for FVC in the oldest group (aged 71–80 years; 1.7% [range: 0.9–2.3%]) significantly varied compared with the youngest group (1.1% [range: 0.6–1.5%], p = 0.049). (**C**) The median CV for FEV_1 in stage 3 or 4 COPD (2.5% [range:1.7–5.4%]) significantly varied compared with that in stage 1 COPD (1.1% [range: 0.8–2.0%], p = 0.001) and stage 2 COPD (2.4% [range: 1.2–3.4%], p = 0.003). (**D**) The median CV for FEV_1 in the oldest group (aged 81–90 years; 1.8% [range:1.8–6.0%]) significantly varied compared with the other groups (1.6% [range: 0.9–2.0%], p = 0.043; 1.6% [range: 0.8–2.3%], p = 0.003; and 2.0% [range: 1.1–3.1%], p = 0.046). Data were presented as median (IRQ).

FVC, we did not find any significant training effect in any age groups. In terms of long-term training effects, we further examined with data at the first visit, which had been obtained 3 years before, in the same 85 subjects. The average CV value for FEV_1 was 2.2 ±1.7%, which was exactly the same as 2.2 ±1.8% in the current study.

Several studies have evaluated short-term variability,[13] between-day variability,[5,7,9] within-day variability,[5,10] and even serial-measurement variability[5,6,8,9,11,12] in healthy participants and those with asthma or COPD. However, the results were remarkably different from those in the current study. Data from previous studies were not subject to the current criteria of the ATS/ERS in which three acceptable curves are required to collect data ideally. Airway stability can vary even within a day in COPD

and asthma, and the magnitude of variability among the three acceptable MEFV curves obtained via one-time measurement is not similar to that of within-day variability. Although several classical studies have examined the serial-measurement variability, they were calculated in simple repeated trials on healthy volunteers at a specific time.

A study examined short-term variability for COPD for six times at an interval of 2–3 weeks. Results showed that the CVs were 11.1% (range: 4.3–25.9%) for FVC and 14.8% (range: 4.8–50%) for FEV_1.[13] In another study that assessed between-day variability for COPD, the CV was 11.66% for FEV_1.[5] Even in healthy participants, the between-day variability, and serial-measurement variability were about 3.0% for FVC and 2.3–3.0% for FEV_1. All

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Table 3 Results of the Stepwise Analysis on the Correlation Coefficient for the Intra-Individual Variability in FVC and FEV_1

Variables	Coefficient	p value
FVC (Log CV, %)		
pre-BD %FEV_1	−0.335	0.005
FEV_1 (Log CV, %)		
Age	0.238	0.008
pre-BD %FEV_1	−0.377	0.001
%LAV	−0.28	0.006

Abbreviations: CV, coefficient of variation; FVC, forced expiratory capacity; BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; LAV, low attenuation volume.

Table 4 $dFEV_1$ in the Different Stages of COPD

	Stage 1	Stage 2	Stage 3 or 4
No	28	36	21
Number of $dFEV_1$ is over 100mL, N (%)	6 (21.4%)	6 (16.7%)	2 (9.5%)
$dFEV_1$, mL	60.7 ± 35.6	59.2 ± 36.5	48.1 ± 32.5

these values were significantly higher than those in our COPD population.[5,7,8,10,11]

FEV_1 and FVC had good reproducibility. However, some factors were associated with higher variability. Stanescu et al examined the serial-measurement variability in the indices of flow–volume curves in patients with COPD.[6] However, their report focused only on PEF, FEF_{50}, and FEF_{75}, not on FVC and FEV_1. Moreover, there were no significant differences in variability in those parameters between patients and healthy controls.

Notably, in this study, a lower %LAV, independent of baseline %FEV_1, was associated with a lower reproducibility of FEV_1. Chronic airflow limitation, which is a characteristic of COPD, is caused by a combination of small airway disease and loss of elastic recoil due to emphysema. Thus, the data in the current study may suggest that small airway pathology itself is more responsible for greater variability in FEV_1 compared with emphysema, when patients with COPD have equal levels of airflow limitation. Another potential explanation might be presence of mucus plug in the airways and instability of airway tonus in the proximal airways in non-emphysema phenotype.

The MCID is an important concept when evaluating longitudinal changes in FEV_1 and/or the effects of pharmacotherapy in COPD. In cases of COPD, the MCID for FEV_1 was 100 mL.[22] In this study, the difference between the maximal and minimal FEV_1 values even among the three acceptable trials was more than this threshold in 14.1% of the participants. This result was observed regardless of spirometric stage. This should be kept in mind when interpreting spirometric data in participants with COPD.

This study had some limitations. First, we exclusively chose participants who underwent spirometry at our hospital, and the tests were conducted by well-trained technicians. Thus, the data in this study could not be universally extrapolated. Second, the sample size was not large enough and moreover not determined based on power calculation. However, to the best of our knowledge, this is the first study that examined the variability of spirometric data derived from three acceptable MEFV curves at one time.

In conclusion, both FVC and FEV_1 values derived from three acceptable MEFV curves are highly reproducible in patients with COPD. Nevertheless, old age and low FEV_1 at baseline, particularly in patients with non-emphysema phenotype, are factors for high variability in FEV_1. Furthermore, the variability in FEV_1 even in one test may be greater than the MCID in some subjects.

Abbreviation

GOLD, the Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; CV, coefficient of variation; PEF, peak expiratory flow rate; FEF_{50}, forced expiratory flow at 50% of expired FVC; FEF_{75}, forced expiratory flow at 75% of expired FVC; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; LAV, low attenuation volume.

Statement of Ethics

The ethics committee of Hokkaido University School of Medicine approved the study protocol (approval number: 02-001), and a written informed consent was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Role of Sponsors

Disclosure

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