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【 ORIGINAL ARTICLE 】

Usefulness of a Newly Developed Spirometer to Measure Dynamic Lung Hyperinflation following Incremental Hyperventilation in Patients with Chronic Obstructive Pulmonary Disease

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Abstract:

Objective This study was performed to determine the usefulness of a newly developed spirometer for the quantitative assessment of dynamic lung hyperinflation (DLH) following incremental hyperventilation in chronic obstructive pulmonary disease (COPD).

Methods The subjects were 54 patients with COPD and 25 healthy volunteers. Each subject was asked to hyperventilate for 30 seconds with stepwise increments starting at the resting respiration rate and increasing to respiratory rates of 20, 30, and finally 40 breaths/min while using a newly developed spirometer. The relationship between the observed inspiratory capacity (IC) reduction following incremental hyperventilation as an index of DLH and spirometry or the 6-minute walking distance was examined.

Results The IC did not decrease significantly from the resting IC, even when the respiratory rate was increased, in the healthy volunteer group. However, in the COPD patient group, the IC decreased with increases in the respiratory rate. Significant correlations were found between all IC parameters and the severity of COPD. A significant negative correlation was also found between the decreased IC and the 6-minute walking distance.

Conclusion These findings suggest that the quantitative assessment of DLH following incremental hyperventilation using the newly developed spirometer may be useful for the assessment of pathophysiological impairment in patients with COPD.

Key words: spirometer, dynamic lung hyperinflation, airflow obstruction, exercise capacity, hyperventilation

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Introduction

Dynamic lung hyperinflation (DLH) is considered to be an especially important factor affecting dyspnea on effort and exercise tolerance (1). In chronic obstructive pulmonary disease (COPD) patients, the decrease in lung elastic recoil pressure and narrowing of the peripheral bronchial lumen have been considered to induce DLH during exercise. In this condition, the inspiratory capacity (IC) is reduced, and the end-expiratory lung volume (EELV) is increased by air trapping following the increase in ventilation (2, 3). The reduced IC limits the increase in tidal volume (TV), which results in unavoidable increases in the respiratory rate, and then the EELV further increases because DLH depends on the respiratory rate (4). The limited potential for increases in TV and the increased workload associated with breathing (5) result in an intensification of the sensation of dyspnea. This mechanism has been suggested to be an important factor involved in the induction of dyspnea on effort and decreased exercise tolerance in COPD patients (4).

FEV_1 has been used to evaluate the severity of airflow obstruction. However, dyspnea on effort, exercise tolerance, and the quality of life (QOL) cannot be determined based

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solely on the FEV_1. Indeed, COPD patients with the same severity of FEV_1 sometimes show different features of degree of dyspnea, exercise capacity, and deterioration of the QOL (6). Furthermore, the improvement in dyspnea or exercise tolerance following intervention with pharmacotherapies has been shown to be closely correlated with DLH but not always with an increased FEV_1 (7). Therefore, the assessment of DLH may be important for the management of COPD.

It has been clearly specified in the Japanese COPD guideline that the basic pathology inducing dyspnea on effort is airflow obstruction and DLH, and the reduction of both airflow obstruction and DLH are important targets for the treatment of COPD (8). However, the assessment of DLH is not widely performed, as it is not easy to evaluate DLH. As such, an easier and simpler method of assessing DLH is needed.

Thus far, DLH has been evaluated by the reduction of IC during exercise using a treadmill or ergometer as well as during the 6-minute walking test (6MWT) (9). This method requires the patient's cooperation during exercise in which he or she periodically performs maximum inspiratory effort (10). This periodic maximum inspiration may aggravate dyspnea, especially in patients with severe COPD. Therefore, we have designed and reported a method for quantitatively determining DLH following hyperventilation in which the respiratory rate is incrementally increased without exercise loading (11). We previously reported that long-acting bronchodilators significantly reduced DLH as evaluated by the metronome-paced incremental hyperventilation (MPIH) method along with improvement of airflow obstruction, oxygenation, the QOL, and exercise capacity, especially in cases of emphysema-dominant COPD (12). We also described the additive effects of short-acting beta-2-agonist on treatment with long-acting bronchodilators (13) and the differences in the effects of long-acting muscarinic antagonist (LAMA) and long-acting beta-2-agonist (LABA) on DLH (14).

However, the measurement of DLH requires the availability of a body box. It may be difficult to measure DLH by the MPIH method using a spirometer, which is widely available, because the IC is usually measured as the volume from the EELV just before hyperventilation to the TLC at maximum inspiration just after hyperventilation, and the air-trapped lung volume during hyperventilation cannot be measured. During hyperventilation, the EELV is increased due to DLH in COPD patients. Therefore, the IC following hyperventilation should be measured from the EELV just before the end of hyperventilation to the TLC at maximum inspiration just after hyperventilation.

In the present study, we developed a dedicated spirometer to measure DLH using the MPIH method in cooperation with Fukuda Denshi (Tokyo, Japan) and evaluated the usefulness of this spirometer in patients with COPD.

Materials and Methods

Patients

The study population consisted of patients with mild to severe stable COPD who regularly visited Shinshu University Hospital between 1 March 2016 and 31 August 2017. COPD was diagnosed in accordance with the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria (15). Specifically, the diagnosis was made based on clinical symptoms, physical examination findings, and a respiratory function characterized by irreversible airflow obstruction.

The following patients were excluded from the study: those with unstable COPD with a history of exacerbation or respiratory infection within the past three months, those with a history of lung or thoracic surgery, those with any orthopedic or cardiovascular complications that might influence their exercise performance, those with difficulty understanding and performing the test, those requiring oxygenation while walking, and those with definite complications of asthmatic symptoms.

To achieve matching between the disease and control groups, age-matched healthy volunteers ≥65 years of age with no respiratory disease or respiratory dysfunction were recruited. All subjects were given an adequate explanation of the study and provided their written informed consent. This study was conducted in accordance with the ethical principles for medical research involving human subjects of the Declaration of Helsinki after obtaining approval from the Shinshu University School of Medicine Medical Ethics Committee (approval number: 3463).

Protocol

In all subjects, DLH following hyperventilation was measured after spirometry was performed in a routine treatment setting. For the COPD patients, the 6MWT was performed at the end of the examination.

Development of a spirometer and measurement of DLH following MPIH

We developed a dedicated spirometer for measuring DLH in cooperation with the manufacturer (Fukuda Denshi, Tokyo, Japan) (Fig. 1). The spirometer uses an automatic zero-flow calibration system (Fig. 2A): at the time of inspiration, the flow sensor is connected to a pressure sensor, and at the time of zero compensation the pressure sensor is automatically switched to atmosphere through an electromagnetic valve. Subjects do not need to remove their mouth from the flow sensor because flow correction can be achieved even if the subject is breathing.

The subjects regulated their rate and timing of breathing in accordance with a light-emitting diode (LED) lamp for inspiration and expiration using a buzzer sound in place of a metronome (Fig. 2B). Each subject was asked to take sev-

eral breaths at rest and then perform maximum inspiration followed by gradual maximum expiration (Fig. 2C). The resting IC and vital capacity (VC) were then measured. Next, the subjects breathed in synchronization with a pulsing sound and light for 30 seconds at a respiratory rate of 20 breaths/min (bpm). Finally, the subjects performed maximum inspiration and then maximum expiration. After a 1- to 2-minute pause, the respiratory rate was increased in steps to 30 bpm for 30 seconds and then to 40 bpm for 30 seconds. At the end of each period of hyperventilation, the subjects performed maximum inspiration and expiration, and the IC and VC were measured. The average of the valleys of three breaths just before maximum inspiration was set as the EELV, and the IC was measured from the EELV.

We can also record the process of overexpansion using this system. Three repeated test series can be saved, and the saved values are automatically averaged and displayed on the screen and printed out. The time required for one measurement is approximately 5 minutes including a break of 1 minute; it takes approximately 15 minutes in total when the measurement is repeated 3 times. The IC at rest and at rates of 20, 30, and 40 bpm rates was expressed as the IC at rest (IC_{rest}), IC_{20}, IC_{30}, and IC_{40}, respectively. DLH was evaluated from the decreases in the IC or the percentage change from the IC_{rest} to IC_{20} ($-IC_{20}$; IC_{20}-IC_{rest}), to IC_{30} ($-IC_{30}$; IC_{30}-IC_{rest}), and to IC_{40} ($-IC_{40}$; IC_{40}-IC_{rest}).

Figure 1. The developed spirometer for the measurement dynamic lung hyperinflation by metronome-paced incremental hyperventilation.

6MWT

The 6MWT was performed using a method that complied with the ATS Guidelines (16). Ambulatory percutaneous oxygen saturation (SpO_2) and pulse rates were recorded us-

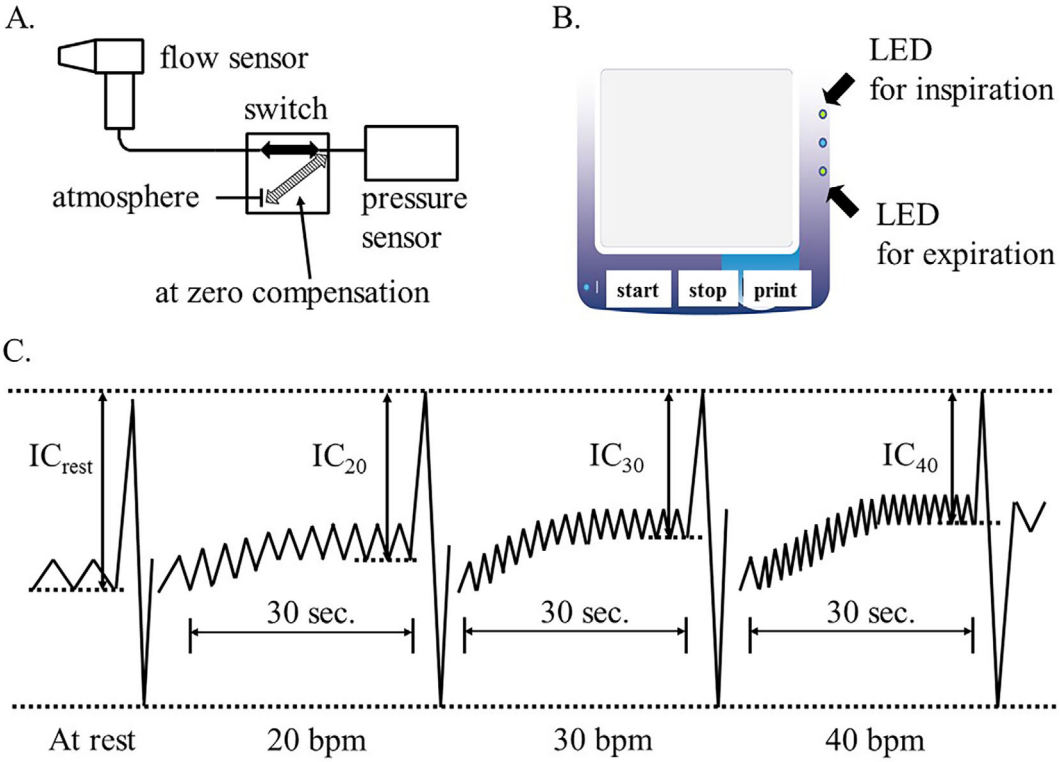

Figure 2. (A) The automatic zero-flow calibration system. At the time of inspiration, the flow sensor was connected to a pressure sensor. At the time of zero compensation, the pressure sensor was automatically switched to atmosphere through an electromagnetic valve. (B) Screen of the spirometer. The rate and timing of breathing were regulated by an LED lamp for inspiration and expiration with a buzzer sound in place of a metronome. (C) Procedure for the measurement of dynamic lung hyperinflation by metronome-paced incremental hyperventilation. LED: light-emitting diode, IC: inspiratory capacity, bpm: breaths/minute

Table 1. Characteristics and the Pulmonary Function Test.

	Healthy volunteers	COPD
n	25	54
Age, years	70.5±1.4	78.4±2.0**
Sex (male/female)	21/4	54/0
Smoking history, pack×year	14.3±3.6	50.6±5.5**
NS, n	14	2
PS, n	11	47
CS, n	0	5
BMI, kg/m^2	23.2±0.6	22.3±0.4
VC, %	106.5±3.1	105.1±2.2
IC, L	2.38±0.12	2.32±0.06
FEV_1, L	2.64±0.13	1.67±0.08**
FEV_1, %	99.2±4.2	63.9±2.6**
FEV_1/FVC, %	77.9±0.9	51.6±1.8**
GOLD stage (1, 2, 3, 4)		12/30/9/3
Treatment with inhaled agents		
LAMA, n		6
LABA, n		4
LAMA+LABA, n		19
LABA+ICS, n		4
LAMA+LABA+ICS, n		6

Values represent the means±standard error of the mean; **p<0.01 vs. Healthy volunteers.

BMI: body mass index, NS: never smoker, PS: past smoker, CS: current smoker, LAMA: long-acting muscarinic antagonist, LABA: long-acting beta 2 agonist, ICS: inhaled corticosteroid

ing a pulse oximeter capable of automatic remote monitoring (wrist-worn pulse oximeter, WristOX$_2$™, Model 3150; Philips Electronics Japan, Tokyo, Japan). All patients were instructed to walk at their fastest speed for the furthest distance they could manage during a 6-minute period. All patients had previously performed this examination and had practiced these exercises. The walking distance (m), SpO_2, heart rate, and modified Borg scale (BS) rating before and immediately after the walking test were analyzed.

Statistical analyses

A sample size of at least 50 patients was calculated to be necessary to detect the correlation between IC reduction as an index of DLH and spirometry or the 6-minute walking distance (6MWD) (power=80%, effect size=0.4, two-sided significance level=5%). In previous studies, healthy volunteers have already been clarified that DLH does not occur. In this study, to confirm that DLH does not occur in healthy volunteers, we set the number of healthy volunteers to half of COPD patients. The values in the text, tables, and figures are shown as the means±standard error of the mean. The Mann-Whitney *U* test was used for the comparison of various parameters between COPD patients and healthy volunteers. Spearman's rank correlation coefficient was used for the bivariate correlation analysis of the IC, IC changes, percentage IC change with percentage FEV_1, and 6MWD. These statistical analyses were performed using the SPSS software program, version 22 (SPSS, Chicago, USA). In all analyses, $p<0.05$ was taken to indicate statistical significance.

Results

Table 1 shows the characteristics, results of spirometry, GOLD stage, and details of current inhaled treatments in patients with COPD. The severity of COPD was widely distributed, and more than half of the patients were classified as moderate severity.

Fig. 3 shows the actual DLH measurements following incremental hyperventilation in one healthy volunteer and one severe COPD patient. The healthy volunteer showed no changes in the EELV or IC when the respiratory rate was incrementally increased from that at rest to 40 bpm, but the patient with severe COPD showed an increased EELV and decreased IC depending on the increase in the rate of hyperventilation.

Table 2 shows the DLH following MPIH in both groups and the results of the 6MWT for COPD patients. The healthy volunteers did not show any changes in the IC when the respiratory rate was incrementally increased, and significant differences were found only between $-IC_{20}$ and $-IC_{30}$ or $-IC_{40}$ and between ΔIC_{20} and ΔIC_{30} or ΔIC_{40}. In contrast, in COPD patients, the IC was significantly decreased in a stepwise manner following hyperventilation, depending on the increase in the rate of breathing, and the IC_{40} was significantly lower than that in healthy volunteers. Both the decreases and changes in IC at 30 and 40 bpm from IC_{rest} were significant greater in COPD patients than in healthy volunteers (Fig. 4).

In COPD patients the mean 6MWD was 468±15 m (range: 121 to 625 m), and the SpO_2 value decreased from 95.7±0.2% before test to 88.4±0.6% after test, indicating mild to moderate desaturation. The correlation coefficients of a simple linear regression analysis between the DLH and FEV_1, 6MWD, or maximum modified Borg scale (BS_{max}) are shown in Table 3. The IC at rest and IC following hyperventilation at all breathing rates and the decreases and changes in IC at all rates from IC_{rest} showed significant positive correlations with the severity of airflow obstruction and the 6 MWD. The correlation coefficient between the FEV_1 and 6 MWD was 0.41, which was lower than the correlations between the parameters of DLH and the 6MWD. Some indexes of DLH also showed weak but significant correlations with the BS_{max}.

Fig. 5 shows scatter plots of the correlation rates among the IC_{30} and $\%FEV_1$ (Fig. 5A) or 6MWD (Fig. 5B) and changes in the IC at 30 bpm from IC_{rest} (ΔIC_{30}) and $\%FEV_1$ (Fig. 5C) or 6MWD (Fig. 5D).

Discussion

Exercise load tests with ergometers have revealed DLH in more than 80% of patients with at least moderate COPD (1)

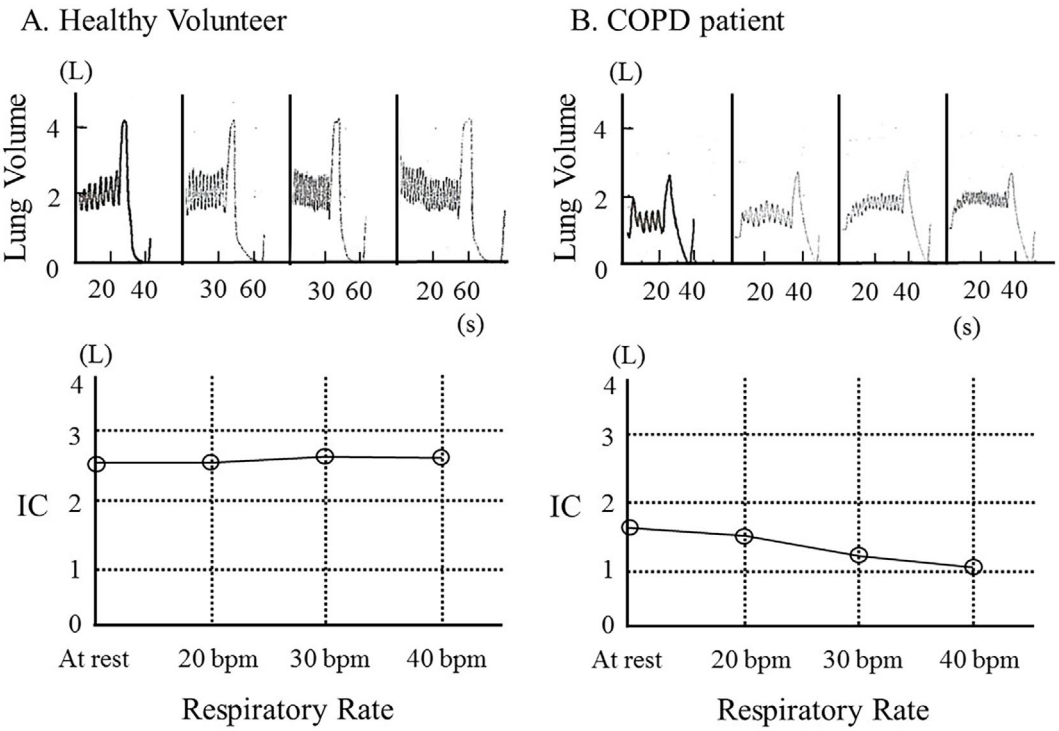

Figure 3. **Measurement of dynamic lung hyperinflation following incremental hyperventilation in a healthy volunteer (A) and a COPD patient (B). The COPD patient showed an incremental decrease in the IC from the value at rest following an incremental increase in respiratory rate, whereas the healthy volunteer showed no change in the IC following hyperventilation. COPD: chronic obstructive pulmonary disease, bpm: breaths/minute, IC: inspiratory capacity**

and showed that even mildly affected patients with no subjective symptoms experience DLH and decreased exercise tolerance (17). The improvement in dyspnea on effort or exercise tolerance following pharmacotherapeutic intervention has been shown to be closely correlated with the improvement of DLH, although it is not always correlated with the improvement of airflow obstruction (7).

Marin et al. (18) reported that the changes in the IC before and immediately after the 6MWT were significantly correlated with changes in the dyspnea scale. With our method, the walking capacity was significantly correlated with both the IC at all respiratory rates and the changes in the IC at all respiratory rates from the value at rest; furthermore, the assessment of DLH following MPIH was able to predict the exercise capacity.

However, weak but significant correlations were found between some parameters of DLH and the maximum BS score during the 6MWT. Comparing the maximum breathlessness during the 6MWT and the degree of DLH dependent on the breathing rate and ventilation following MPIH may not be reasonable, as breathlessness during the 6MWT may be dependent on effort, and the maximum breathing rate and breathing pattern may differ. We recently reported that the relief of airflow obstruction by treatment with LAMA resulted in an increase in the walking distance but did not improve the maximum BS score (12-14). All parameters of DLH showed significant correlations with the FEV_1; however, the correlation coefficients were not very high. DLH induced by exercise load has been shown to be most closely correlated with the diffusion capacity, and patients with the emphysema-dominant phenotype of COPD had a significantly faster rate of DLH occurring early in exercise than those with a preserved diffusion capacity (1). We also reported that the emphysema-dominant phenotype showed more prominent DLH following MPIH than those with the emphysema non-dominant phenotype (12). Therefore, DLH is suggested to be dependent on not only airflow obstruction but also the collapsibility of small airways during tidal breathing resulting from the decreased elastic recoil pressure.

We previously measured DLH via the MPIH method using a body box, and the EELV and IC were measured by body plethysmography immediately after hyperventilation (11). However, the body box system is expensive and not widely available. Therefore, a cheaper and easier-to-use apparatus for measuring DLH is required. We developed a dedicated spirometer for the measurement of DLH by the MPIH method. The measurement method resembles that of a spirometer, and the technician needs no special training to perform the procedure. However, this system is slightly more expensive than a spirometer.

The most devised point of developing the spirometer was determining of the level of EELV just after the end of 30-s hyperventilation and to measure the maximum inspiration from that point. The second point was the adaptation of an automatic zero-flow calibration system to correct instances

Table 2. Dynamic Lung Hyperinflation Following Hyperventilation and 6-minutewalking Test (6MWT).

	Healthy volunteers	COPD patients
n	25	54
IC_{rest}, L	2.44±0.11	2.38±0.06
IC_{20}, L	2.45±0.10	2.31±0.08
IC_{30}, L	2.35±0.11	2.16±0.08††
IC_{40}, L	2.34±0.11	2.02±0.09*††
$-IC_{20}$, L	0.01±0.07	-0.07±0.04
$-IC_{30}$, L	-0.09±0.07††	-0.23±0.05††
$-IC_{40}$, L	-0.10±0.07††	-0.36±0.05**††
ΔIC_{20}, %	2.1±3.1	-3.3±1.9
ΔIC_{30}, %	-2.8±2.9††	-10.0±2.1*††
ΔIC_{40}, %	-3.3±2.9††	-15.8±2.4**††
6MWD, m		468±15
Pre SpO_2, %		95.7±0.2
Lowest SpO_2, %		88.4±0.6
Pre PR, bpm		72.8±1.7
PR_{max}, bpm		114.2±2.3
Pre BS		0.3±0.1
BS_{max}		4.6±0.3

Values represent the means±standard error of the mean; *p<0.05 and **p<0.01 vs. healthy volunteers; †p<0.05 and ††p<0.01 vs. $-IC_{20}$ or ΔIC_{20}.

IC: inspiratory capacity, bpm: breaths/min, IC_{rest}: IC at rest, IC_{20}: IC at 20 bpm, $-IC_{20}$: decrease in IC from IC_{rest} to IC_{20}, ΔIC_{20}: change in IC from IC_{rest} to IC_{20}, IC_{30}: IC at 30 bpm, $-IC_{30}$: decrease in IC from IC_{rest} to IC_{30}, ΔIC_{30}: change in IC from IC_{rest} to IC_{30}, IC_{40}: IC at 40 bpm, $-IC_{40}$: decrease in IC from IC_{rest} to IC_{40}, ΔIC_{40}: change in IC from IC_{rest} to IC_{40}, SpO_2: percutaneous oxygen saturation, PR_{max}: maximum pulse rate, BS_{max}: maximum modified Borg scale, 6MWD: 6-minute walking distance

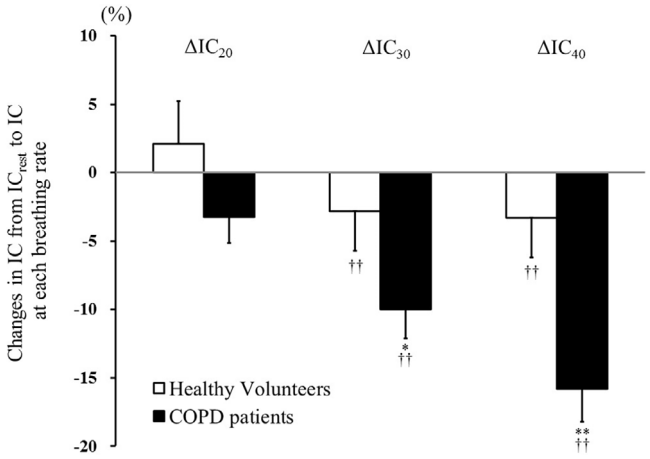

Figure 4. Changes in the IC from the value at rest to IC_{20}, IC_{30}, and IC_{40} in healthy volunteers and patients with COPD. *p<0.05 vs. healthy volunteer: †p<0.05 and ††p<0.01 vs. ΔIC_{20}. IC: inspiratory capacity, IC_{rest}: IC at rest, IC_{20}: IC at 20 breaths/min, ΔIC_{20}: change in the IC from the IC_{rest} to IC_{20}, IC_{30}: IC at 30 breaths/min, ΔIC_{30}: change in the IC from the IC_{rest} to IC_{30}, IC_{40}: IC at 40 breaths/min, ΔIC_{40}: change in the IC from the IC_{rest} to IC_{40}

Table 3. Correlation Coefficients in Simple Linear Regression Analysis between the Parameters of Dynamic Lung Hyperinflation and the Severity of Airflow Limitation, the 6-minute Walking Distance (6MWD), or Maximum Modified Borg Scale (BS_{max}).

	$\%FEV_1$(%)	6MWD (m)	BS_{max}
IC_{rest}	0.34**	0.36**	-0.07
IC_{20}	0.47**	0.55**	-0.24
IC_{30}	0.49**	0.55**	-0.26
IC_{40}	0.54**	0.54**	-0.27*
$-IC_{20}$	0.33**	0.50**	-0.27*
$-IC_{30}$	0.38**	0.40**	-0.23
$-IC_{40}$	0.41**	0.36**	-0.24
ΔIC_{20}	0.37**	0.51**	-0.30*
ΔIC_{30}	0.43**	0.45**	-0.27*
ΔIC_{40}	0.47**	0.44**	-0.27

*p<0.05 and **p<0.01.

IC: inspiratory capacity, bpm: breaths/min, IC_{rest}: IC at rest, IC_{20}: IC at 20 bpm, $-IC_{20}$: decrease in IC from IC_{rest} to IC_{20}, ΔIC_{20}: change in IC from IC_{rest} to IC_{20}, IC_{30}: IC at 30 bpm, $-IC_{30}$: decrease in IC from IC_{rest} to IC_{30}, ΔIC_{30}: change in IC from IC_{rest} to IC_{30}, IC_{40}: IC at 40 bpm, $-IC_{40}$: decrease in IC from IC_{rest} to IC_{40}, ΔIC_{40}: change in IC from IC_{rest} to IC_{40}

of zero flow without having the patient remove their mouth from the flow sensor. The spirogram at each respiratory rate was displayed, and the ΔIC was calculated automatically and printed out. The EELV quickly increased and became stable by 20 seconds in most COPD patients. The subjects regulated the rate and timing of breathing using an LED lamp for inspiration and expiration and a buzzer sound in place of a metronome. In the present study, the incrementally increased rate of breathing was set as 20, 30, and 40 bpm, as in our previous reports. O'Donnell et al. (19) reported that the rate of breathing at which the increase in TV was limited was 27 bpm during symptom-limited cycle exercise, and the rate then rapidly increased and reached a maximum of approximately 35 bpm in patients with moderate to severe COPD. Therefore, the incremental rates of breathing determined in this study were considered to be appropriate.

However, several limitations associated with the present study warrant mention. First, we have not yet confirmed the maximum rate during the 6MWT. Second, $PaCO_2$ reduction following hyperventilation may lead to contraction of the bronchial smooth muscle (20, 21). Third, we did not compare the DLH measurements obtained using our newly developed spirometer with those obtained conventionally during the 6MWT. This remains to be investigated in the future.

Conclusion

The quantitative assessment of DLH by the MPIH method using our newly developed spirometer may aid in evaluating the pathophysiological impairment in patients with COPD and support the management of this disease.

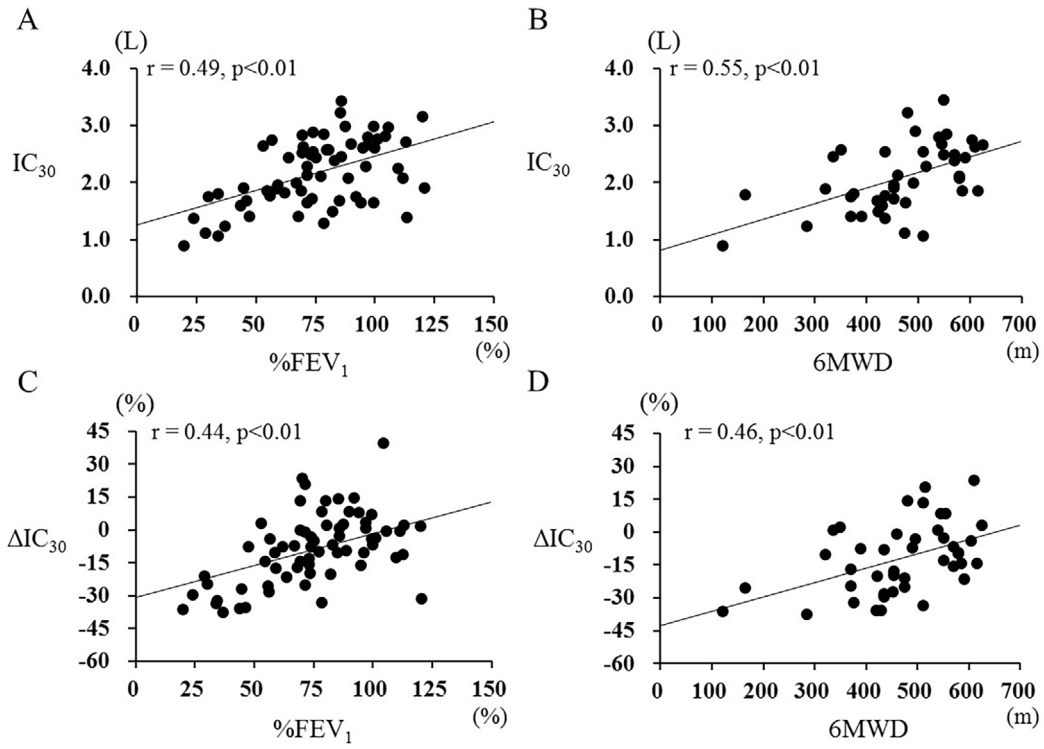

Figure 5. Correlations between the IC_{30} and $\%FEV_1$ or 6MWD (A and B) and between the ΔIC_{30} and $\%FEV_1$ or 6MWD (C and D). IC_{30}: inspiratory capacity (IC) following 30-s hyperventilation at 30 breaths/min, ΔIC_{30}: change in the IC at rest to IC_{30}, 6MWD: 6-minute walking distance

The authors state that they have no Conflict of Interest (COI).

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