

Correlation between Bronchodilator Responsiveness and Quality of Life in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Guidelines and literature debate the importance of testing for bronchial reversibility and its total significance is unclear. Clinically, patients with greater reversibility have higher fluctuations in respiratory symptoms, and hence may have a reduced health-related quality of life (HRQoL). On the other hand, they may have a better HRQoL as medications may be more effective in this population. Presently, there are no reports concerning the relationship between HRQoL as an indicator of therapy and reversibility. We hypothesized that the reversibility of airflow limitation might be correlated with the HRQoL in COPD.

Methods: We examined 63 subjects with COPD (mean age: 71.7 years). Reversibility was measured by the change in FEV1 and FVC after the inhalation of salbutamol (300 µg), and we investigated the relationship between the reversibility and the parameters of HRQoL, which included St. George's Respiratory Questionnaire (SGRQ), Visual analogue scale-8 (VAS-8), Short-Form 36-Item Health Study, Basic activities of daily living, Instrumental activities of daily living, and the Oxygen cost diagram.

Results: Post-bronchodilator FEV1, % predicted was positively correlated with both the total scores of SGRQ and VAS-8 ($p < 0.0001$ and $p < 0.006$, respectively). Furthermore, the reversibility of FVC was positively correlated with all items of the SGRQ, except for impact (total score: $p < 0.02$; symptoms: $p < 0.02$; activity, $p < 0.05$; total score of VAS-8: $p < 0.02$). However, the reversibility of FEV1 was neither correlated with the total score nor any items in the scales.

Conclusions: Those who have FVC that respond to bronchodilator at rest might result in an improvement of HRQoL after treatment.

KEY WORDS

activities of daily living, airflow limitation, bronchodilator reversibility, COPD, health-related quality of life (HRQoL)

INTRODUCTION

The role of bronchodilator reversibility (BDR) in chronic obstructive pulmonary disease (COPD) is important in establishing a diagnosis and determining therapeutic strategies.¹⁻³ According to recent ATS/ERS guidelines,² the objectives for bronchodilator reversibility tests are as follows: exclusion of bronchial asthma in the diagnosis of COPD, measurements of the best and highest values for the pulmonary func-

tion test, prediction of the outcome, and determination of therapeutic strategies. However, the efficacy of long-acting bronchodilators cannot be predicted from that of short-acting bronchodilators.¹⁻³ The significance of BDR on outcomes is ill-defined. HRQoL is one measure of outcomes in COPD patients. Clinically, patients with greater reversibility have higher fluctuations in respiratory symptoms, which may adversely affect their health-related quality of life (HRQoL). On the other hand, the benefit from medi-

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cines may be greater in patients with a higher BDR, resulting in an improved HRQoL. To our knowledge, no previous study concerning the relationship between HRQoL as an indicator of therapy and bronchial reversibility has been reported.

Standard guideline consensus for bronchodilator reversibility has not yet been obtained. Two major issues are likely warranted in this regard. First, a standard calculation formula has not been determined,^{4,6} and second, the clinical indications or applications for reversibility data need to be clarified. The response to inhaled bronchodilators can be assumed by measuring lung functions, usually FEV₁, before and after drug administration.^{1,3} This may be a useful test; however, it should not be used as an absolute guide for the administration of a bronchodilator since the response to bronchodilators on a particular occasion may not accurately reflect responses at other times.⁷ Moreover, there is no consensus as to what constitutes a significant response to bronchodilator therapy, with any cut-off point being arbitrary in COPD.⁸ Substantial evidence suggests that 'reversibility' is a continuous variable rather than a dichotomous trait.⁹ However, since forced vital capacity (FVC), slow vital capacity (SVC), inspiratory capacity (IC), and exercise tests show better correlations with symptoms in COPD,¹⁰⁻¹³ there is good reason to measure response rather than FEV₁ in such patients. In the present study, we hypothesized that reversibility of airflow limitations might be correlated with the health-related quality of life in COPD.

METHODS

The subjects were 63 consecutive patients who initially consulted the outpatient clinic at the Respiratory Care Clinic, Nippon Medical School, Tokyo, Japan, for ambulatory treatment. Eligible patients fulfilled the following criteria: 1) patients whose clinical course, clinical symptoms, and laboratory data satisfied criteria for the clinical diagnosis of COPD,¹ and 2) those with a life-long history of smoking, including current and ex-smokers.

We excluded those:

- 1) with a history of atopy, or those with any apparent asthmatic features
- 2) receiving any corticosteroid regimens
- 3) with exacerbations during the preceding three months
- 4) with cognitive disorders, as assessed using the mini-mental state examination (MMSE),¹⁴ with a score less than 26
- 5) with other respiratory diseases such as bronchiectasis or any pulmonary fibrosis or cardiac disorders

This study was approved by the Ethics Committee of the institute, and the subjects were enrolled after appropriate informed consent was obtained.

LUNG FUNCTION TESTS AND REVERSIBILITY OF AIRFLOW LIMITATIONS

Patients were told to abstain from bronchodilators (BD), including any types of β_2 agonists and/or anticholinergic regimen, for 12 hours before testing. There were no cases that received tiotropium at this stage. Spirometry was performed before, then 20 minutes after an administration of 300 μ g of salbutamol (Glaxo Smith Kline, UK), using a meter-dose inhaler with an inhalation chamber (715 ml). The best record of three measurements was used for the analysis. FVC was measured via forced expiration for at least six seconds. In cases of older participants, appropriate attention was paid to the technique as described previously.¹⁵ The reversibility by salbutamol inhalation was calculated for both FEV₁ and FVC, in addition to the air trapping index. The reversibility of FEV₁ was calculated by the following formula:¹⁶ $([\text{post-BD FEV}_1 - \text{pre-BD FEV}_1]/\text{pre-BD FEV}_1) \times 100\%$.

The reversibility of FVC was similarly defined. The air trapping index was calculated using the following equation: $(\text{VC-FVC}) \times 100/\text{VC}$.

QUALITY OF LIFE AND ACTIVITIES OF DAILY LIVING

All of the patients were measured for a generic and health-related quality of life (HRQoL) on the same day that the lung function test was performed. These included St George's Respiratory Questionnaire (SGRQ),¹⁷ Short-Form 36-Item Health Study (SF-36),^{18,19} and the Visual analogue scale-8 quality of life (VAS-8 QOL).^{20,21} Activities of daily living (ADL) were evaluated using items from the basic activities of daily living (BADL)²² and the instrumental activity of daily life (IADL),²³ while dyspnea on exertion was evaluated using items from the oxygen cost diagram (OCD).²⁴ Japanese versions of SGRQ and OCD were used in this study.^{25,26}

To assess exercise capacity, the six-minute walking distance test (6MWD) was applied using the standard protocol.²⁷

OTHER CLINICAL TESTING

Arterial blood gas was simultaneously measured while room air was breathed in a supine position. To exclude co-morbidity including heart failure, chest X-ray (posterior-anterior direction), ECG, and blood chemistry were performed.

STATISTICS

All results are expressed as means \pm SEM. Group means were compared by analysis of variance (ANOVA) followed by a multiple comparison of means by Fisher's least-significance procedure. All statistical tests were two-tailed and $p < 0.05$ was considered significant. To investigate the relationship between reversibility and HRQoL, linear regression

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Table 1 Patient characteristics.

n (n = 63)	Male (n = 56), Female (n = 7)		
Age (yr) (M/F)	71.7 ± 0.9 (70.0–73.4)	(72.0 ± 0.9/69.4 ± 0.9)	
	Pre-bronchodilator	Post-bronchodilator	Difference
FVC	2.42 ± 0.08 (2.26–2.58)	2.66 ± 0.08 (2.51–2.81)	0.24 ± 0.03 (0.18–0.30)
FEV1	1.28 ± 0.07 (1.15–1.41)	1.38 ± 0.07 (1.38–1.51)	0.10 ± 0.02 (0.07–0.13)
FEV1/FVC	51.9 ± 1.55 (48.8–55.0)	51.4 ± 1.68 (48.0–54.7)	–0.53 ± 0.57 (–1.67–0.60)
FEV1, %predict	51.6 ± 2.65 (46.3–56.9)	55.7 ± 2.70 (50.3–61.1)	4.08 ± 0.63 (2.81–5.34)
Arterial blood gas			
pH	7.42 ± 0.004	(7.41–7.43)	
PaCO ₂ (mmHg)	42.8 ± 0.58	(41.6–43.9)	
PaO ₂ (mmHg)	74.5 ± 1.19	(72.1–76.9)	
6MD (m)	415.4 ± 14.1	(386.9–443.9)	
ADL			
BADL	20.0 ± 0.03	(19.9–20.0)	
IADL	26.4 ± 0.42	(25.5–27.2)	
OCD	80.3 ± 2.45	(75.4–85.1)	
SF-36			
Physical-function	70.9 ± 2.76	(65.4–76.4)	
Role-physical	58.6 ± 5.51	(47.6–69.6)	
Body-pain	75.2 ± 2.98	(69.3–81.2)	
General health	50.9 ± 2.84	(45.2–56.5)	
Vitality	62.8 ± 2.95	(56.9–68.7)	
Social	81.4 ± 3.00	(75.3–87.4)	
Role-emotional	53.0 ± 6.72	(39.6–66.4)	
Mental health	69.2 ± 3.00	(63.2–75.2)	
PCS	44.8 ± 1.14	(42.6–47.1)	
MCS	47.1 ± 1.44	(44.2–49.9)	

Definition of abbreviations: 6MD = six-minute walking distance test; ADL = Activities of daily living; BADL: Basic activities of daily living; IADL = Instrumental activities of daily living; 6MD = six-minute walking distance test; OCD = Oxygen cost diagram; SF-36 = Short-Form 36-Item Health Study; PCS = Physical Cornell Summary; MCS = Mental Cornell Summary.

Table 2 Correlation between post-bronchodilator FEV₁, % predicted and the health-related quality of life.

SGRQ		
Total SGRQ score	<i>p</i> < 0.0001	<i>r</i> ² = 0.300
Symptoms	<i>p</i> < 0.0007	<i>r</i> ² = 0.119
Activity	<i>p</i> < 0.0001	<i>r</i> ² = 0.338
Impact	<i>p</i> < 0.0006	<i>r</i> ² = 0.169
VAS-8 QOL		
Total	<i>p</i> < 0.006	<i>r</i> ² = 0.239
Dyspnea	<i>p</i> < 0.04	<i>r</i> ² = 0.143
Social activity	<i>p</i> < 0.05	<i>r</i> ² = 0.118
Housework or job	<i>p</i> < 0.002	<i>r</i> ² = 0.188
Appetite	<i>p</i> < 0.01	<i>r</i> ² = 0.121
Anxiety	<i>p</i> < 0.005	<i>r</i> ² = 0.145

Definition of abbreviations: SGRQ = St George's Respiratory Questionnaire; VAS-8 QOL = Visual analogue scale-8 quality of life.

analysis was applied, taking the Pearson correlation coefficient as a measure of the extent of the relationship. Calculations for statistical analysis were performed using SPSS 11.0 (SPSS Inc.; Illinois, 2001).

RESULTS

Participant characteristics are shown in Table 1. A total of 63 subjects, consisting of 56 men and 7 women, with a mean age of 71.7 years, were studied; there were no significant differences in age between men and women. Mean values of reversibility in FEV₁ (Δ FEV₁) and FVC (Δ FVC) were 9.6% and 11.4%, respectively. Post-bronchodilator FEV₁, % predicted was positively correlated with the following items of SGRQ: total score (*p* < 0.0001, *r*² = 0.300), symptoms (*p* < 0.0007, *r*² = 0.119), activity (*p* < 0.0001, *r*² = 0.338), and impact (*p* < 0.0006, *r*² = 0.169) (Table 2). In addition, post-BD FEV₁, % predicted was positively correlated with the following items of VAS-8QOL: total score (*p* < 0.006, *r*² = 0.239), dyspnea (*p* < 0.04, *r*² =

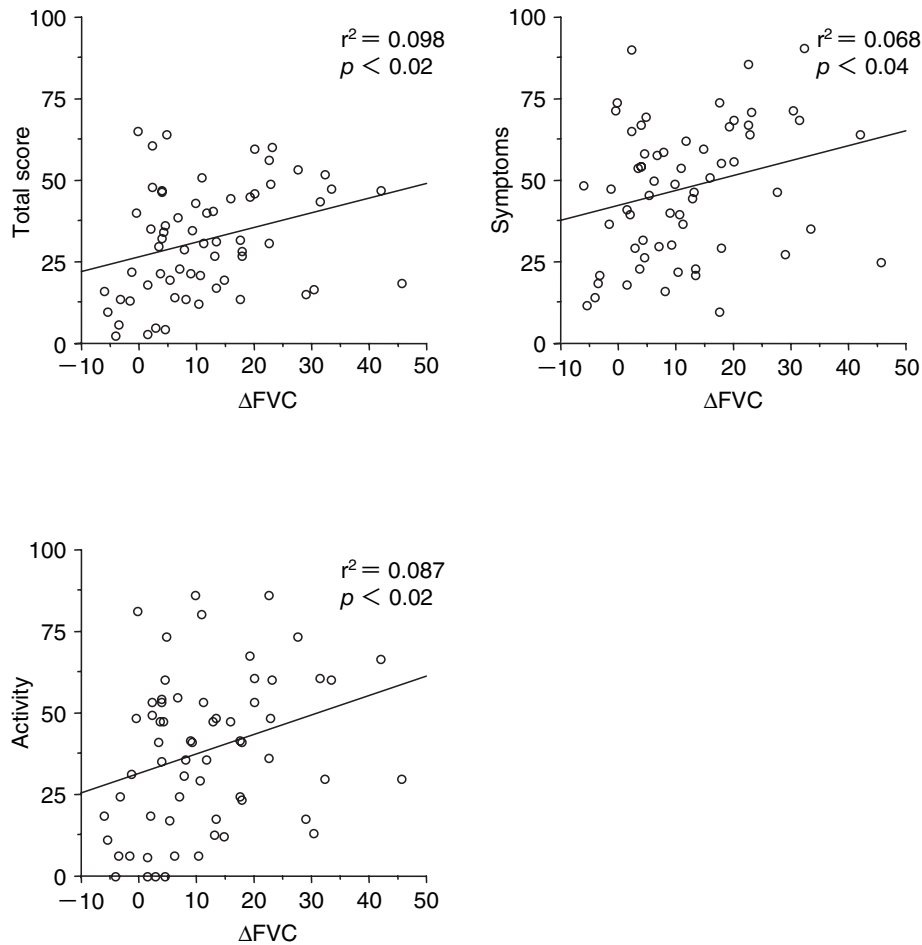


Fig. 1 Relationship between the reversibility of forced vital capacity and St. Georges's Respiratory Questionnaire. Δ FVC was positively correlated with all SGRQ items except for impact.

0.143), social activity ($p < 0.05$, $r^2 = 0.118$), housework or job ($p < 0.002$, $r^2 = 0.188$), appetite ($p < 0.01$, $r^2 = 0.121$), and anxiety ($p < 0.005$, $r^2 = 0.145$) (Table 2). However, neither the volume nor the percentage of FEV1 reversibility was positively correlated with any item of SGRQ, VAS-8 QOL, or SF-36, nor with BADL, or IADL.

Figure 1 shows the relationship between Δ FVC and SGRQ items. Δ FVC was positively correlated with all SGRQ items except for impact (total score, $p < 0.02$, $r^2 = 0.098$; symptoms, $p < 0.02$, $r^2 = 0.068$; activity, $p < 0.05$, $r^2 = 0.087$).

Figure 2 indicates the relationship between the reversibility of FVC (Δ FVC) and VAS-8 QOL items. Δ FVC was positively correlated with the following items of VAS-8 QOL: total score ($p < 0.02$, $r^2 = 0.100$), dyspnea ($p < 0.002$, $r^2 = 0.177$), social activities ($p < 0.05$, $r^2 = 0.072$), and headache ($p < 0.04$, $r^2 = 0.079$). Δ FVC was correlated with OCD ($p < 0.002$, $r^2 = 0.159$), the social functioning of SF-36 ($p < 0.02$, $r^2 =$

0.101), and the air trapping index ($p < 0.005$, $r^2 = 0.128$) (Table 3). However, Δ FVC was not correlated with either BADL or IADL. Although the air trapping index was not correlated with Δ FEV1, it was positively correlated with Δ FVC ($p < 0.005$, $r^2 = 0.128$). The air trapping index was not correlated with any item of VAS-8QOL; however, it was positively correlated with the following items of SGRQ: total score ($p < 0.006$, $r^2 = 0.118$), symptoms ($p < 0.05$, $r^2 = 0.066$), activity ($p < 0.03$, $r^2 = 0.083$), and impact ($p < 0.02$, $r^2 = 0.094$). For SF-36, it was positively correlated with body pain ($p < 0.006$, $r^2 = 0.124$) and the physical component summary (PCS) ($p < 0.04$, $r^2 = 0.070$).

There was no correlation between Δ FVC and the six-minute walking distance test (6MWD), and no correlation between reversibility in FEV1 and the 6MWD was observed.

DISCUSSION

The present study investigated bronchodilator re-

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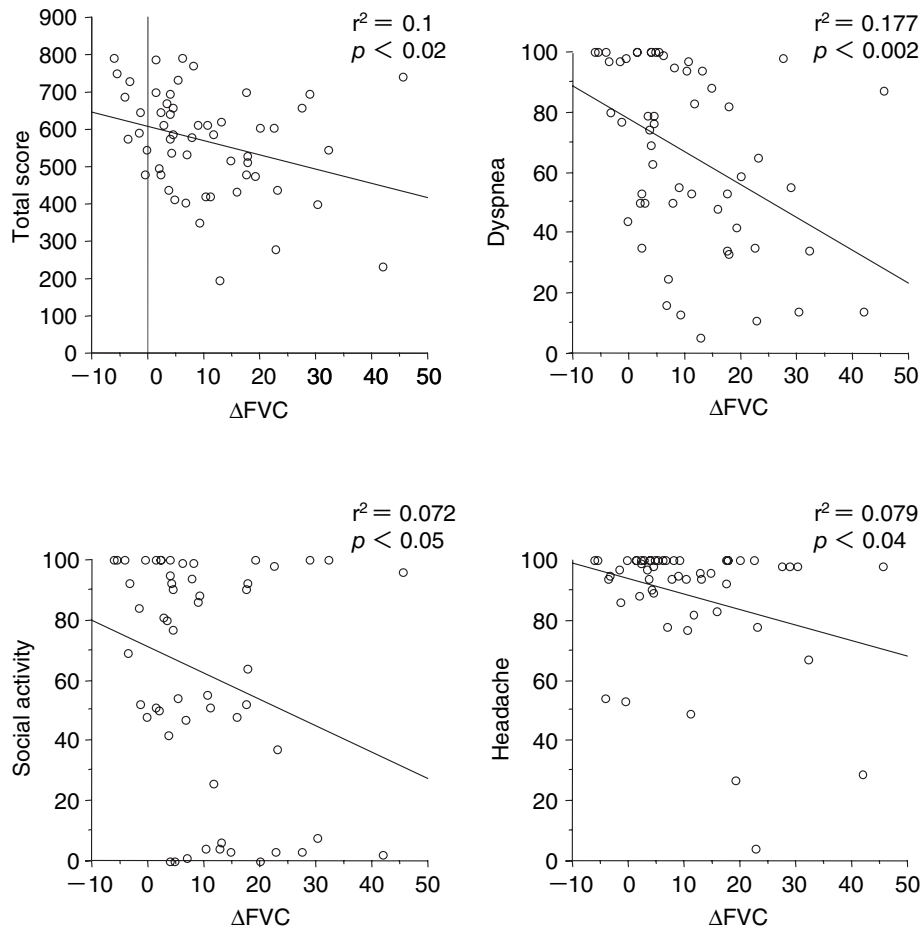


Fig. 2 Relationship between the reversibility of forced vital capacity and visual analogue scale-8 QOL. Reversibility of FVC was positively correlated with the following items of VAS-8 QOL: total score ($p < 0.02$, $r^2 = 0.100$), dyspnea ($p < 0.002$, $r^2 = 0.177$), social activities ($p < 0.05$, $r^2 = 0.072$), and headache ($p < 0.04$, $r^2 = 0.079$).

Table 3 Correlation between the reversibility of forced vital capacity and other factors.

SGRQ		
Total score	$p = 0.0126$	$r^2 = 0.098$
Symptoms	$p = 0.0387$	$r^2 = 0.068$
Activity	$p = 0.0192$	$r^2 = 0.087$
VAS-8 QOL		
Total score	$p = 0.0188$	$r^2 = 0.100$
Dyspnea	$p = 0.0014$	$r^2 = 0.177$
Social activity	$p = 0.0469$	$r^2 = 0.072$
Headache	$p = 0.0371$	$r^2 = 0.079$
OCD	$p = 0.0012$	$r^2 = 0.159$
SF-36		
Social functioning	$p = 0.0124$	$r^2 = 0.101$
Air trapping index	$p = 0.0040$	$r^2 = 0.128$

Definition of abbreviations: SGRQ = St George's Respiratory Questionnaire; VAS-8 QOL = Visual analogue scale-8 quality of life; OCD = Oxygen cost diagram; SF-36 = Short-Form 36-Item Health Study

versibility in stable COPD, and reported a cross-sectional relationship between bronchodilator reversibility and the respective items of the health-related QOL and activities of daily living.

The present study showed several interesting findings. Δ FVC was positively correlated with HRQoL, as shown in Figure 1 and 2. The air trapping index was significantly and positively correlated with Δ FVC, and also with many items in the HRQoL.

Newton *et al.* reported that a relatively low dose of inhaled salbutamol reduces hyperinflation and gas trapping in patients with significant baseline hyperinflation, often to a remarkable degree, even in patients with advanced disease.²⁸ Figure 3 shows the detailed correlations among HRQOL items, Δ FVC, Δ FEV1, and the air trapping index. Items showing a correlation are represented by circles, while those without a correlation are represented by \times . It is possible that these reflect an improvement in pulmonary hyperinflation. According to the present results, air trapping

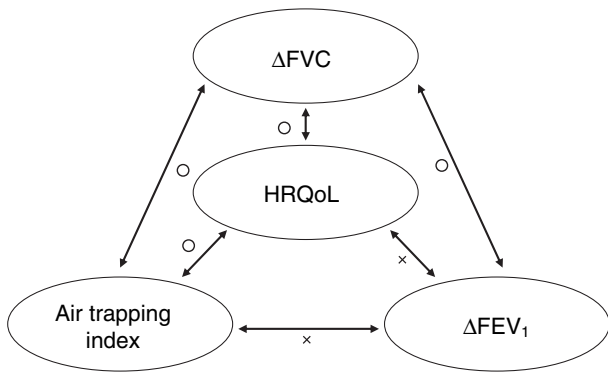


Fig. 3 Possible relationship between QOL and pulmonary function. Detailed correlations among HRQoL items, Δ FVC (the reversibility of FVC), Δ FEV₁ (the reversibility of FEV₁), and the air trapping index. Items showing a correlation are represented by ○, while those without a correlation are represented by ×.

in COPD might be the contributing factor for the decrease in HRQoL. The improvement of FVC might suggest the improvement of air trapping, and may reflect the significant correlation between the reversibility of FVC and HRQoL.

However, several points in the study design, which might have influenced the results, should be pointed out. First, the subjects involved in this study were limited to patients with stable COPD. In addition, more than 90% of the subjects were 65 years old or older. Previous studies have demonstrated that the level of salbutamol-induced bronchodilator response decreases with age, although the level of ipratropium-induced bronchodilator response is not influenced by age.^{29,30} However, Nisar and associate report³¹ that the influence of age on the bronchodilator response is limited, and suggest that this may reflect the progression of the disease rather than an age-related difference in the number of receptors.

Second, the dose of salbutamol was fixed in this study. Previous reports^{32,33} suggest that the inhalation of salbutamol at a dose higher than 300 μ g facilitated the differentiation of asthmatic patients from chronic bronchitic patients. Moreover, most data from the dose-response by salbutamol in COPD patients suggest that the inhalation of 800 μ g of salbutamol induces a maximal or near maximal response.³⁴ Since the subjects in our study were shifted towards the elderly (mean age: 71.7 years), 300 μ g of salbutamol was inhaled to avoid the occurrence of adverse effects on the cardiovascular system with the perspective of application in daily clinical practice.

Third, we used the pre-bronchodilator value of FEV₁, which was conventional, to evaluate the reversibility of FEV₁. This tends to show that patients with severe COPD will exhibit stronger bronchodilator responses.³⁵

When a formula is used that divides the predicted value of FEV₁, which was proposed by Anthonisen *et al.*⁴ and Eliasson *et al.*,³³ it suggests that expressing the results of reversibility tests as the degree of variation does not produce mathematical biases. Furthermore, it is speculated that the degree of variation of reversibility is influenced by physical characteristics such as gender, age, and height, or a previous clinical course such as acute exacerbations, where the patient might be receiving systemic corticosteroid. There is substantial debate about the most appropriate method of calculating the reversibility of FEV₁.⁴⁻⁶

Fourth, inspiratory capacity (IC) measured by plethysmography might be required to determine reversibility more precisely. Using absolute or percentage changes in FEV₁ might underestimate bronchodilator reversibility in COPD. Two reasons for this are that 1) dynamic airway collapse occurs during forced expiration, and 2) it is likely that many more subjects with COPD would have had a significant BDR if slow and unforced vital capacity maneuvers had been used.^{35,36}

In this study, we did not measure the response of IC before and after salbutamol inhalation, because the present study aimed to clarify the significance of routine clinical application by spirometry use (based on FVC with forced expiration over at least six seconds).

O'Donnell *et al.*³⁷ performed spirometry and constant-volume body plethysmography. Despite its disadvantages, spirometry is easy to perform and is widely used in routine clinical settings. On the other hand, during body plethysmography, it is important to maintain oral and alveolar pressures at an equal level, though this is not always possible. In particular, it might be hard to maintain the quality of pressure in patients with airway obstruction. In such cases, higher values for the intrathoracic gas volume can be obtained by dynamic changes in the upper airway when panting is performed under the condition of increased airway resistance. It is a likely disadvantage that this error increases with the severity of airway obstruction.³⁸ However, reversibility using body plethysmography should be conducted in the future for further evaluation.

According to Newton *et al.*,²⁸ regardless of whether the choice for a volume response is governed by the convenience of using a spirometric index such as FVC or by the intent of maximizing the effect by adding IC and RV, the volume effects are relatively similar after bronchodilator administration.

The measurement of FVC in COPD patients remains controversial. ATS statements in 1991 suggested that the total expiration time should be considered for evaluating FVC as a bronchodilator response, as patients with obstructive pulmonary disease show a prolonged expiration time and increased FVC.³⁹ Thus, we adopted a forced expiration for over

six seconds for measuring FVC. In their study, William *et al.* reported⁴⁰ that the response after increases in FEV3 and FEV6 may be a secure bronchodilator response, and that the significance of a response occurring after the increase in FVC alone remains unclear, as this increase in FVC is due to the prolonged expiration time. Considering the results of the study reported by William *et al.*,⁴⁰ it is preferable to use FEV6 as an index instead of FVC for bronchodilator response in the future.

It has been reported that changes in FEV1 after the inhalation of β 2-agonists in COPD patients were not associated with an improvement in the perception of dyspnea.^{10,12,41} Changes in FEV1 were limited to a narrow range whereas the reversibility of FVC was widely distributed. These findings support a notion that a better health-related QOL can be obtained in COPD patients by exhaling as much breath as possible during expiration. The present study suggests that the bronchodilator-induced reversibility of FVC is associated with HRQoL. This was supported by the findings that Δ FVC was positively correlated with SF-36 and changes in OCD as well as SGRQ and VAS-8 QOL. Since our study population was small, the present findings need to be further evaluated in a larger patient population.

As summarized in Figure 3, there was a correlation between the reversibility in FEV1 and in FVC; however, no correlation was noted between the air trapping index and the reversibility in FEV1. As COPD progressed, destruction of both supporting tissue and elastic fibers in the lung result in reduced recoil and tethering, which increased airway resistance and expiratory flow limitation. In patients with COPD, inhalation of the short-acting β -agonist, salbutamol, reduce symptoms without improving the FEV1^{10,12} which suggest that the airway diameter in resting respiration may be improved, or functional residual capacity (FRC) may decrease the work to be done by inspiratory muscles. The distance achieved after walking for 6 minutes increased after bronchodilator administration, and this may have been attributed to an improvement of FVC, rather than FEV1. Since an increase in FVC decreases resting FRC, which may reduce the range of dynamic hyperinflation during exercise.²⁸ More recently, O'Donnell *et al.*⁴² reported that inhalation of a long-acting cholinergic regimen resulted in consistent improvements in trough FEV1 compared to a placebo, with little or no change in the FEV1/FVC ratio. They observed that the slight changes in FEV1 mainly reflect the increase in FVC. An increased vital capacity (VC) is inversely related to decreased residual volume (RV), which occurs as result of complete lung emptying. Improvement of dyspnea on exertion in COPD after inhalation of the regimen was attributed to a decrease in RV and an increase in inspiratory capacity (IC) rather than an improvement of FEV1; thus, they concluded that the ef-

fect is due to an improvement of dynamic hyperinflation. Although these results support the notion, the precise reason why no correlation was observed between the air trapping index and reversibility in FEV1 in this study remains to be clarified, and requires further study.

Since the spirogram suggested that FVC was FEV6,⁴⁰ FEV1 reversibility may be correlated with FVC reversibility.

Our results from the reversibility tests for airway obstruction for both FEV1 and FVC are likely to provide useful information. In addition, the measurement of reversibility in FVC may become a useful clinical marker in terms of HRQoL. This supports the usefulness of pursed-lip expiration and bronchodilators for COPD treatment.⁴³

In conclusion, the improvement of FVC by β -agonist inhalation might be closely correlated with the health-related quality of life; thus, this measurement might provide different clinical information from the reversibility of FEV1.

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