

Pretreatment with inhaled procaterol improves symptoms of dyspnea and quality of life in patients with severe COPD

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Background: The clinical efficacy of short-acting β_2 -agonists administered before performing daily activities in chronic obstructive pulmonary disease (COPD) is unclear. The aim of this study was to investigate the clinical effect of supplementary inhaled procaterol hydrochloride in patients with COPD.

Methods: Thirty outpatients with moderate to severe COPD (Stage II–IV) regularly using inhaled tiotropium bromide alone and with dyspnea during daily activities were enrolled. Subjects self-administered 20 μ g of inhaled procaterol before daily activities no more than four times daily. Dyspnea symptom scores, St George's Respiratory Questionnaire (SGRQ) activity domains, impulse oscillometry system parameters, and pulmonary function tests were recorded at the beginning and end of the 2-week study.

Results: At baseline, more than 80% of subjects reported dyspnea when walking up a slope (100.0%), climbing stairs (100.0%), gardening (93.3%), walking on flat ground (90.0%), bathing (86.7%), getting on a bus or train (83.3%), and changing clothes (80.0%). After 2 weeks, subjects with Stage III symptoms had significantly improved dyspnea scores on walking up a slope ($P = 0.047$), climbing stairs ($P = 0.014$), gardening ($P = 0.034$), walking on flat ground ($P = 0.006$), getting on a bus or train ($P = 0.039$), and changing clothes ($P = 0.045$). Both symptom and activity SGRQ domains improved significantly in subjects with Stage III symptoms ($P = 0.036$ and $P = 0.028$, respectively). Resistance of small airways and low-frequency reactance area values improved significantly in subjects with Stage III symptoms ($P = 0.003$ and $P = 0.004$, respectively). No significant changes were found in pulmonary function tests.

Conclusion: Use of supplementary inhaled procaterol before performing daily activities improved dyspnea symptoms in subjects with Stage III COPD.

Keywords: chronic obstructive pulmonary disease, impulse oscillometry system, procaterol, daily activities, quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible narrowing of the peripheral airways and decreased elastic recoil pressures in the peripheral airways due to destruction of alveoli. As a result, air is trapped in peripheral areas of the lung, especially during exercise. This dynamic hyperinflation relates significantly to symptoms of dyspnea during exercise, and decreases exercise tolerance and ability to perform daily activities.^{1,2}

Patients with COPD often avoid daily activities which bring on dyspnea, and as a result, their ability to perform these activities worsens, along with their quality of life. In particular, patients with severe COPD (Stage IV) who need home oxygen therapy often

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avoid leaving the home and are inactive. Pitta et al reported that patients with COPD spend significantly less time walking and standing, have significantly lower movement intensity during walking, and spend significantly more time sitting and lying down compared with healthy subjects.³ Pulmonary rehabilitation, defined as exercise training for at least 4 weeks with or without education and/or psychological support, can improve exercise capacity and quality of life in patients with COPD. According to 23 randomized controlled trials in the Cochrane database, pulmonary rehabilitation can relieve dyspnea and fatigue, improve emotional function, and provide COPD patients with a sense of control over their illness.⁴ However, because not all patients with COPD are able to benefit from exercise training, pharmacological support should be also considered.⁵

According to treatment guidelines, such as those of the Global Initiative for Chronic Obstructive Pulmonary Disease⁶ and the Japanese Respiratory Society,⁷ long-acting anticholinergic agents, such as tiotropium bromide and long-acting β_2 -agonists, are recommended as first-line drugs for the treatment of COPD. The effects of long-acting β_2 -agonists occur 30–60 minutes after administration, so use of a short-acting β_2 -agonist is recommended for cases of sudden dyspnea. Because repeated episodes of sudden dyspnea in COPD patients can worsen quality of life, emotional state, and ability to perform physical activities, occurrences of sudden dyspnea should be minimized and ideally eliminated.

The aims of the present study were to evaluate the effect of inhaled procaterol (a short-acting β_2 -agonist) administered immediately before performing daily activities to reduce symptoms of dyspnea in subjects with COPD, and to examine the relationship between dyspnea symptoms, quality of life, and status of the peripheral airways before and after 2 weeks of use of supplementary inhaled procaterol.

Methods

Subjects

The study protocol was approved by the institutional ethics committee of Tohno-Kousei Hospital, carried out in

accordance with the principles of the Helsinki Declaration, and registered in the UMIN clinical trials registry system (<http://www.umin.ac.jp>). The clinical importance, purpose, and possible disadvantages of participation in the study were explained in detail to each subject prior to enrolment, and informed consent was obtained. Subjects were outpatients with Stage II (moderate) to Stage IV (very severe) COPD, according to the guideline of the Japanese Respiratory Society.⁷ This guideline uses a spirometric classification of disease severity based on the % predicted forced expiratory volume in 1 second (FEV₁) value: Stage I (mild), FEV₁ $\geq$ 80% predicted; Stage II (moderate), 50% $\leq$ FEV₁ < 80% predicted; Stage III (severe), 30% $\leq$ FEV₁ < 50% predicted; and Stage IV (very severe), FEV₁ < 30% predicted.

Inclusion criteria were a diagnosis of COPD Stage II, III, or IV, presence of dyspnea on at least one ordinary daily activity, and regular use of inhaled tiotropium bromide alone for more than 6 months. Because we wanted to evaluate the clinical efficacy of a short-acting β_2 -agonist, we excluded patients with COPD who regularly used long-acting β_2 -agonists. Patients who met the following criteria were also excluded: present smokers and exsmokers who had quit in the previous year; treatment with other short-acting β_2 -agonists in the previous 3 months; treatment with oral or intravenous corticosteroids in the previous 3 months; home oxygen therapy initiated in the previous 6 months; presence of other chronic respiratory disease; currently taking medication for chronic respiratory tract infection; presence of severe hepatic, heart, renal, or hematologic disease or other grave complications; and history of poor drug compliance. Patients were also excluded if participation in the study was deemed inappropriate by a medical doctor. Patient characteristics are shown in Table 1.

Measurements

All subjects completed a questionnaire about the degree of dyspnea (0 = no symptoms; 5 = very severe dyspnea) experienced during 15 kinds of daily activities at the start and end of the study, as shown in Table 2. This questionnaire was derived from that used in a study reported by

Table 1 Patient characteristics

	Total	Stage II	Stage III	Stage IV
Numbers of patients	30	9	10	11
Gender (M/F)	28/2	8/1	9/1	11/0
Mean age (yr)	76.4 $\pm$ 5.8	74.2 $\pm$ 6.3	76.6 $\pm$ 4.9	78.1 $\pm$ 6.3
Past smoking history (yr)	44.3 $\pm$ 10.5	45.9 $\pm$ 15.2	45.7 $\pm$ 8.0	41.8 $\pm$ 8.1
Pack-year	62.3 $\pm$ 26.9	55.9 $\pm$ 25.0	54.4 $\pm$ 25.8	68.7 $\pm$ 25.1

Table 2 Dyspnea occurrence rates and symptom scores by daily activity and COPD stage

Kind of daily activity	Occurrence rates of dyspnea (N = 30)	Dyspnea score																	
		Stage II (N = 9) (%)					Stage III (N = 10) (%)					Stage IV (N = 11) (%)							
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Climbing a slope	100.0 (%)	0.0	11.1	22.2	33.3	11.1	22.2	0.0	0.0	0.0	10.0	20.0	70.0	0.0	0.0	0.0	18.2	18.2	63.6
Going up stairs	100.0 (%)	0.0	22.2	11.1	33.3	22.2	11.1	0.0	0.0	0.0	10.0	10.0	80.0	0.0	0.0	9.1	9.1	18.2	63.6
Gardening	93.3 (%)	22.2	0.0	44.4	0.0	33.3	0.0	0.0	0.0	10.0	10.0	30.0	50.0	0.0	0.0	9.1	18.2	9.1	63.6
Walking on flat ground	90.0 (%)	33.3	11.1	22.2	11.1	0.0	22.2	0.0	10.0	10.0	20.0	30.0	30.0	0.0	27.3	27.3	9.1	9.1	27.3
Taking a bath	86.7 (%)	33.3	22.2	33.3	0.0	11.1	0.0	10.0	10.0	20.0	20.0	10.0	30.0	0.0	0.0	27.3	18.2	27.3	27.3
Getting on a bus or train	83.3 (%)	33.3	33.3	22.2	11.1	0.0	0.0	10.0	10.0	20.0	10.0	10.0	40.0	9.1	18.2	18.2	9.1	9.1	36.4
Changing clothes	80.0 (%)	66.6	22.2	11.1	0.0	0.0	0.0	10.0	30.0	20.0	30.0	10.0	0.0	0.0	18.2	27.3	27.3	27.3	0.0
Making bed	73.3 (%)	55.5	22.2	0.0	11.1	11.1	0.0	20.0	0.0	20.0	30.0	0.0	30.0	9.1	0.0	18.2	36.4	0.0	36.4
Toilet	66.7 (%)	55.5	22.2	22.2	0.0	0.0	0.0	30.0	10.0	30.0	10.0	10.0	10.0	18.2	0.0	54.5	9.1	18.2	0.0
Cleaning room	63.3 (%)	44.4	11.1	11.1	22.2	11.1	0.0	40.0	0.0	10.0	20.0	0.0	30.0	27.3	0.0	18.2	18.2	9.1	27.3
Eating	56.7 (%)	66.6	33.3	0.0	0.0	0.0	0.0	40.0	10.0	20.0	20.0	10.0	0.0	27.3	27.3	18.2	27.3	0.0	0.0
Brushing teeth	56.7 (%)	77.7	22.2	0.0	0.0	0.0	0.0	20.0	10.0	60.0	0.0	10.0	0.0	36.4	9.1	18.2	18.2	18.2	0.0
Shaving	53.3 (%)	88.8	11.1	0.0	0.0	0.0	0.0	30.0	10.0	50.0	10.0	0.0	0.0	27.3	18.2	27.3	27.3	0.0	0.0
Cooking	46.7 (%)	77.7	0.0	11.1	0.0	0.0	11.1	40.0	20.0	0.0	10.0	0.0	30.0	45.5	0.0	18.2	27.3	0.0	9.1
Getting up in the morning	43.3 (%)	77.7	11.1	11.1	0.0	0.0	0.0	30.0	20.0	40.0	10.0	0.0	0.0	63.6	18.2	0.0	18.2	0.0	0.0

Notes: %Scores of severity of dyspnea symptom: 0, none; 1, slightly; 2, mild; 3, moderate; 4, severe; 5, very severe.

Eakin et al.⁸ Subjects chose 3–4 daily activities during which severe dyspnea was always felt. Before performing the chosen daily activities, subjects were instructed to inhale 20 µg of procaterol hydrochloride (Meptin® 10 µg, Otsuka Pharmaceutical Industry, Tokyo, Japan), a third-generation short-acting β_2 -agonist. Subjects were instructed to inhale procaterol a maximum of four times a day (two inhalations twice per day, with at least 4 hours between use) and record when and how many times each day they used procaterol. Before the start of the study, each patient learned how to inhale a short-acting β_2 -agonist and was also instructed on how to use the inhalation device properly. It was confirmed that each subject had no adverse reactions to procaterol, such as an increase in heart rate, before starting the study.

At the beginning and the end of the 2-week study, subjects completed a COPD-specific questionnaire, ie, the St George's Respiratory Questionnaire (SGRQ),⁹ concerning their quality of life. The SGRQ consists of 76 questions, and replies are categorized into three domains, ie, symptoms, activity, and impact. The total score is calculated as the overall SGRQ. A minimal clinically important difference on the SGRQ is achieved if four scores improve from the beginning to the end of the study. Permission to use the SGRQ was obtained from Dr K Nishimura (Respiratory Division, Murakami Memorial Hospital, Gifu, Japan), who assumes the editorship of the Japanese version.

At the beginning and end of the study, components of central and peripheral airway resistance were tested using an impulse oscillometry system. The MastersScreen IOS-J (Erich JAEGER, Hoechberg, Germany) measures respiratory resistance using an oscillation technique in which impulse signals at frequencies of 0–100 Hz are produced by a loudspeaker. The flow and mouth pressure are then measured to analyze respiratory impedance. The device processes impulse waves by fast Fourier transform in real time and analyzes respiratory resistance, impedance, reactance, and resonance frequency in the airway, lung, and thorax. Measurements at 5–35 Hz provide the viscosity, inertia, and elastic resistance associated with respiratory resistance. The impulse oscillometry system parameters, R5 and R20, represent resistance of the whole airway and central airway, respectively. The R5–R20 reactance at 5 Hz and low-frequency reactance area values reflect distal airway resistance. The impulse oscillometry system can be applied noninvasively to patients during resting respiration over 4–5 breaths, and the components of resistance in the central and peripheral airways can be separated. The impulse oscillometry system has been used for childhood asthma

and COPD patients in Europe and the US.^{10,11} Shiota et al recently reported that impulse oscillometry system results have satisfactory reproducibility.¹² Additionally, pulmonary function indices were measured at the beginning and end of the study using pulmonary function test apparatus (SP-750, Fukuda Electronics, Tokyo, Japan).

Statistical analysis

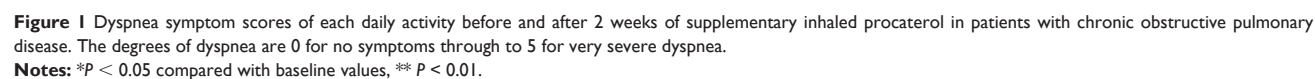
The significance level was set at $P < 0.05$. SGRQ scores and impulse oscillometry system parameters are presented as median values (25–75th percentiles) and pulmonary function indices as means $\pm$ standard deviation. Dyspnea scores, SGRQ scores, and impulse oscillometry system parameters were analyzed using the Wilcoxon signed-rank test. Comparison of pulmonary function values was performed using paired *t*-tests. All statistical analyses were carried out using JMP version 5.0.1A (SAS Institute Inc, Cary, NC).

Results

Thirty patients with COPD ($n = 9$, $n = 10$, and $n = 11$ with Stage II, III, and IV, respectively) were approached at the start of the study. All of them were enrolled and all completed the 2-week study. No adverse effects from the use of inhaled supplementary procaterol, such as tachyphylaxis, were reported during the study. Procaterol was used by each subject a median (25–75th percentile) of 2.00 (1.19–2.32) times per day. Separated into COPD stages, the median value of times per day procaterol used was 2.03 (1.40–2.90) in Stage II, 1.97 (1.07–2.27) in Stage III, and 1.64 (1.27–1.86) in Stage IV subjects. Although the use of procaterol was not statistically different between the COPD stages of severity, the median values for daily use seemed to increase with increasing severity of COPD.

Dyspnea symptom scores

At the start of the study, subjects were questioned about the degree of dyspnea experienced during 15 kinds of daily activities, as shown in Table 2. More than 80% of subjects experienced dyspnea on walking up a slope (100.0%), climbing stairs (100.0%), gardening (93.3%), walking on flat ground (90.0%), bathing (86.7%), getting on a bus or train (83.3%), and changing clothes (80.0%). Dyspnea symptom scores for different daily activities at the beginning and end of the study are shown in Figure 1. In Stage III subjects, dyspnea symptom scores significantly improved for all daily activities except for bathing. Although the changes were not statistically significant, dyspnea scores for all daily activities seemed to improve over the study period in Stage II and IV



subjects, with the exception of a significant improvement in dyspnea symptom scores for getting on a bus or train ($P = 0.034$) in Stage II subjects.

SGRQ scores

SGRQ scores at the beginning and end of the 2-week study period are shown in Figure 2. In subjects with Stage III COPD, scores for symptoms and activity domains significantly improved over the study period. In particular, the symptom score improved by more than four points, and exceeded the minimal clinically important difference score. The SGRQ score in each domain tended to improve in Stage II and IV subjects, but these changes were not significant. In Stage II COPD subjects, all domains of the SGRQ improved by an average of more than four points and exceeded the minimal clinically important difference. In Stage IV COPD subjects, the symptoms score improved by an average of more than four points.

Impulse oscillometry system parameters

Impulse oscillometry system parameters at the beginning and end of the 2-week study period are shown in Figure 3. R5 values, which represent whole airway resistance, significantly improved in Stage III and IV subjects.

R20 values, which reflect resistance in central airways, significantly improved in Stage II and IV subjects. R5–R20 and low-frequency reactance area values, which reflect resistance in the distal airways, significantly improved in Stage III and IV subjects.

Pulmonary function indices

A comparison of pulmonary function indices measured before and after the 2-week study period is shown in Table 3. There were no significant changes in any of the pulmonary function indices in subjects from all COPD stages.

Correlation between parameters

No correlations between dyspnea symptom scores, impulse oscillometry system parameters, SGRQ scores, or pulmonary function parameters were found.

Discussion

This study investigated the clinical efficacy of supplementary inhaled procaterol before performing daily activities in patients with Stage II, III, and IV COPD. The lack of a control group is a significant limitation of this study, as is the small sample size. However, we have shown that use of supplementary inhaled procaterol tends to improve

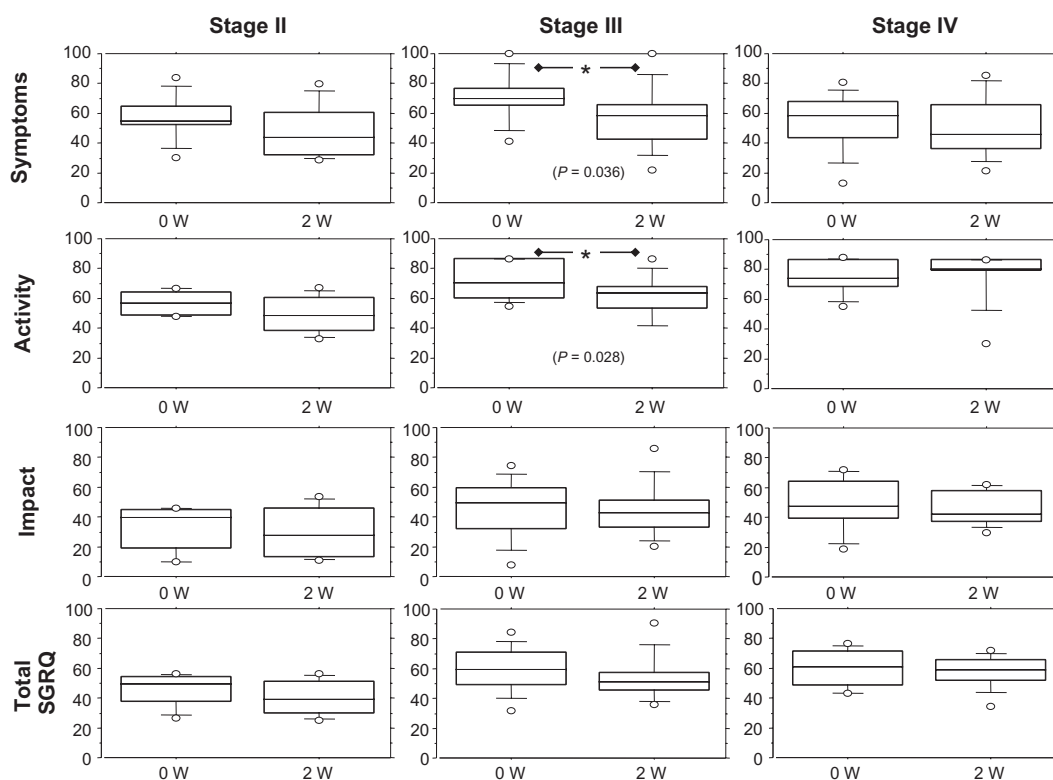


Figure 2 St George's Respiratory Questionnaire scores before and after 2 weeks of supplementary inhaled procaterol in patients with chronic obstructive pulmonary disease. **Note:** * $P < 0.05$ compared with baseline values.

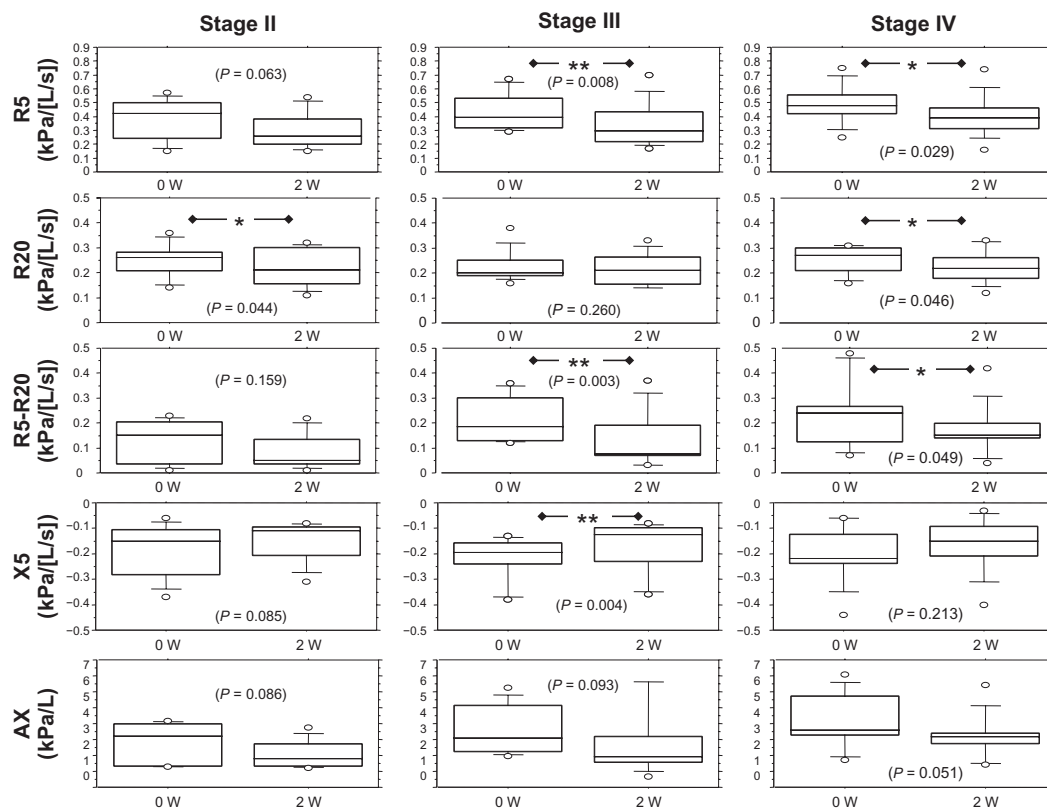


Figure 3 Impulse oscillometry system parameters before and after 2 weeks of supplementary inhaled procaterol in patients with chronic obstructive pulmonary disease. **Notes:** ** $P < 0.01$ and * $P < 0.05$ compared with baseline values.

dyspnea symptoms and quality of life in patients with COPD. Over the 2-week study period, symptoms of dyspnea improved for all daily activities, except for bathing in the Stage III group (Figure 1). Furthermore, the symptom and activity domains of the SGRQ also significantly improved in Stage III subjects (Figure 2). The SGRQ score in both domains improved more than four points, indicating a clinical improvement in quality of life in Stage III subjects. Inhaled supplementary procaterol was an effective therapy for treatment of dyspnea in COPD, particularly for subjects with severe (Stage III) disease.

No significant changes were found in most pulmonary function indices (Table 3). On the other hand, some impulse oscillometry system parameters improved significantly at the end of the 2-week study period (Figure 3). In particular, the significant improvements in R5–R20 and R5–R20 reactance at 5 Hz indices may be of clinical importance. The indices of standard pulmonary function tests, such as FEV_{10} , mainly reflect the condition of the large central airways, and do not adequately reflect the condition of the peripheral airways. Furthermore, because patients in the present study had previously been treated regularly with tiotropium, narrowing of the central airways may have been treated

already. Prior use of this medication may also be a reason why standard pulmonary function indices did not improve significantly. The impulse oscillometry system can describe both central and peripheral airways resistance in COPD,¹³ and significant improvements were seen in whole airway and distal airway indices using this technique in the present study. Considering that dyspnea symptoms in COPD are mainly caused by trapped air in narrowed peripheral airways and destruction of alveoli, the peripheral airway is a therapeutic target in COPD. The particle size of inhaled drugs affects delivery of the drug to the peripheral airways.^{14,15} Compared with the larger particles of powdered tiotropium (almost 5 μ m),¹⁶ the average particle diameter of procaterol is about 2 μ m. Inhaled procaterol particles can reach the peripheral airways and diminish air trapping there.¹⁷ This reduction in damage to the peripheral airways can lead to improvement in symptoms of dyspnea and quality of life.

As mentioned earlier, we found no correlations between dyspnea symptom scores, impulse oscillometry system parameters, SGRQ scores, or pulmonary function parameters. The major reason for this may be that dyspnea symptoms are too complicated to be described only by the present commonly used measurement indices.

Table 3 Average pulmonary function indexes by COPD stage

	0 W	2 W	P value
Stage IV			
%VC (%)	59.7 ± 14.5	61.5 ± 12.9	0.409
IC (L)	1.12 ± 0.36	1.05 ± 0.28	0.743
%FVC (%)	53.5 ± 14.3	53.7 ± 11.8	0.751
FEV1.0-G (%)	43.3 ± 11.2	44.1 ± 12.2	0.623
%FEV1.0 (%)	33.69 ± 10.9	37.8 ± 13.8	0.149
MEFR (L/sec)	0.40 ± 0.28	0.40 ± 0.30	0.417
PEF (L/min)	1.70 ± 0.67	1.92 ± 0.87	0.708
FEF50 (L/sec)	0.35 ± 0.23	0.36 ± 0.18	0.398
FEF75 (L/sec)	0.20 ± 0.08	0.22 ± 0.09	0.085
Stage III			
%VC (%)	84.4 ± 18.2	88.3 ± 22.1	0.211
IC (L)	1.61 ± 0.48	1.73 ± 0.66	0.518
%FVC (%)	76.0 ± 19.3	75.0 ± 21.4	0.625
FEV1.0-G (%)	44.7 ± 6.6	46.5 ± 6.9	0.471
%FEV1.0 (%)	53.8 ± 18.6	55.5 ± 21.8	0.317
MEFR (L/sec)	0.86 ± 0.59	0.95 ± 0.80	0.267
PEF (L/min)	2.58 ± 1.07	2.93 ± 1.38	0.065
FEF50 (L/sec)	0.49 ± 0.21	0.50 ± 0.25	0.678
FEF75 (L/sec)	0.24 ± 0.10	0.29 ± 0.10	0.127
Stage II			
%VC (%)	96.6 ± 12.9	100.5 ± 14.2	0.206
IC (L)	1.79 ± 0.47	1.85 ± 0.52	0.792
%FVC (%)	89.4 ± 12.7	93.0 ± 15.8	0.108
FEV1.0-G (%)	56.1 ± 11.2	59.9 ± 16.1	0.165
%FEV1.0 (%)	78.0 ± 17.2	85.4 ± 26.4	0.086
MEFR (L/sec)	2.16 ± 2.03	2.51 ± 2.16	0.046
PEF (L/min)	3.89 ± 1.71	4.19 ± 1.98	0.078
FEF50 (L/sec)	0.95 ± 0.85	1.16 ± 1.02	0.299
FEF75 (L/sec)	0.46 ± 0.48	0.52 ± 0.52	0.321

Abbreviations: FEF, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; MEFR, mid-expiratory flow rates; PEF, peak expiratory flow; VC, vital capacity.

Finally, this study indicates that use of supplementary inhaled procaterol can significantly improve peripheral airways function in patients with severe COPD (Stage III), can lead to improvement in symptoms of dyspnea brought on by ordinary daily activities, and can enhance quality of life. Supplementary inhaled procaterol may be a useful therapy for prevention of progression of staging in severe COPD.

Disclosure

The authors report no conflicts of interest in this work.

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