Benefits of Oxygen on Exercise Performance and Pulmonary Hemodynamics in Patients With COPD With Mild Hypoxemia*

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Benefits of Oxygen on Exercise Performance and Pulmonary Hemodynamics in Patients With COPD With Mild Hypoxemia*

Keisaku Fujimoto, MD; Yukinori Matsuzawa, MD; Shinji Yamaguchi, MD; Tomonobu Koizumi, MD; and Keishi Kubo, MD, FCCP

Study objectives: To clarify the effects of oxygen on exercise performance and pulmonary hemodynamics during exercise in patients with COPD with mild hypoxemia at rest.

Design: Seventy-five male patients with stable COPD (“pink puffer” type), accompanied by mild hypoxemia (> 60 mm Hg) at rest and with mild (percentage of predicted FEV$_1$ [%FEV$_1$] > 50%, n = 16), moderate (%FEV$_1$ > 35% to ≤ 50%, n = 25), and severe (%FEV$_1$ ≤35%, n = 34) airflow obstruction were recruited from an outpatient clinic. A 6-min walking distance (6MD) test was administered to 75 patients, and the pulmonary hemodynamics of 43 subjects were determined during exercise on a supine bicycle ergometer at 25 W and breathing compressed air and oxygen at 2 L/min.

Results: Supplemental oxygen resulted in a significant increase in 6MD, except for patients with mild airflow obstruction and mild desaturation. This increase in 6MD produced by oxygen was greater as the restriction of the airflow was more severe, and correlated negatively with %FEV$_1$, but not with PaO$_2$ at rest or exercise hypoxemia. Pulmonary artery pressure (Ppa) and pulmonary artery occlusion pressure (Pop) increased with exercise, while the rates of increase in both types of pressure were significantly higher for severe COPD than for mild COPD and moderate COPD. Oxygen inhalation significantly reduced the increases in Ppa and Pop during exercise in patients with moderate-to-severe COPD, and the effect of oxygen on the increase in Pop correlated positively with airtrapping (vital capacity – FVC).

Conclusion: These findings suggest that supplemental oxygen benefits patients with COPD with moderate-to-severe airflow obstruction and mild hypoxemia at rest, as reflected in improvement in exercise performance and pulmonary hypertension during exercise.

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Key words: COPD; dynamic hyperinflation; exercise; oxygen inhalation therapy; pulmonary artery occlusion pressure; pulmonary hemodynamics; walking test

Abbreviations: CI = cardiac index; %FEV$_1$ = percentage of predicted FEV$_1$; LTOT = long-term oxygen therapy; 6MD = 6-min walking distance; Pop = pulmonary artery occlusion pressure; Ppa = pulmonary artery pressure; PVRI = pulmonary vascular resistance index; SpO$_2$ = pulse oximetric saturation; VC = vital capacity

The benefits of long-term oxygen therapy (LTOT) for patients with COPD associated with hypoxemia < 60 mm Hg at rest are well known. LTOT for these patients prolongs survival, reduces the frequency of hospitalization and development of pulmonary hypertension, and improves activities of daily living and quality of life. However, it has not been clearly established whether supplemental oxygen therapy for patients with COPD with mild-to-moderate hypoxemia is beneficial. Some studies found that there was no significant difference in the survival rates of patients with COPD with mild-to-moderate hypoxemia (> 56 mm Hg) with and without LTOT. It was also reported that nocturnal oxygen therapy did not modify the evolution of pulmonary hypertension, and did not result in a delay in the prescription of LTOT for patients with COPD with mild-to-moderate daytime hypoxemia who exhibited sleep-related oxygen desaturation. However, it has been demonstrated that supplemental oxygen during exercise results in acute improvements in exercise tolerance and dyspnea in some patients with COPD with mild hypoxemia at...
However, it has not been clarified in which type of patients with COPD such acute improvement in exercise tolerance and dyspnea is more prominent. The aim of this study was to examine whether supplemental oxygen improves exercise performance and pulmonary hemodynamics during exercise in patients with COPD who show mild hypoxemia at rest, and to determine for which type of patient supplemental oxygen during exercise is more beneficial. We evaluated exercise performance by using a 6-min walking distance (6MD) test, and measured the pulmonary hemodynamics of patients with COPD who showed mild hypoxemia (PaO₂ > 60 mm Hg) and normal PaCO₂ at rest and mild-to-severe airflow obstruction, during exercise with a bicycle ergometer and breathing compressed air and oxygen. We then analyzed the relationship between the effects of oxygen on exercise performance or pulmonary hemodynamics during exercise and the severity of airflow obstruction.

## Materials and Methods

### Patients

Seventy-five male patients with smoking-related stable COPD without α1-antitrypsin deficiency were recruited from our outpatient clinic and enrolled in this study. They showed mild hypoxemia (PaO₂ > 60 mm Hg) and normal PaCO₂ at rest, and mild-to-severe airflow obstruction, the so-called “pink puffer” type of COPD (Table 1). All patients were ex-smokers and had a smoking history of > 30 pack-years. COPD was diagnosed on the basis of a clinical history of exertional dyspnea, pulmonary function testing results that confirmed the presence of irreversible airflow obstruction (FEV₁/FVC < 70% after inhalation of a bronchodilator), lung hyperinflation, decreased diffusion capacity of the lung for carbon monoxide (< 80% of predicted values), and anatomic emphysema observed on high-resolution CT. Patients with any history of asthma or changes in symptoms, those who showed reversibility of ≥ 15% and 200 mL of FEV₁ after inhalation of 20 µg of procaterol hydrochloride, had received inhaled or oral steroids, or had a respiratory tract infection or exacerbation of their airway disease during the preceding 6 weeks were excluded. The patients were classified into three groups according to the COPD guideline criteria proposed by the Japanese Respiratory Society: the “mild” group was defined as showing a percentage of predicted FEV₁ (%FEV₁) > 50%, the “moderate” group as showing a %FEV₁ between 50% and 35%, and the “severe” group showing a %FEV₁ ≤ 35%. On the basis of these criteria, 16 patients were classified into the mild group, 25 patients were classified into the moderate group, and 34 patients were classified into the severe group. All were treated with bronchodilators including regular inhalation of an anti-cholinergic agent and/or β₂-agonists and/or slow-releasing theophylline for > 6 months before the study. The local research ethics committee approved the study, and all patients gave informed consent for administration of pulmonary function tests and the 6MD test. Forty-three patients (6 patients in the mild group, 15 patients in the moderate group, and 22 patients in the severe group) also gave informed consent for the pulmonary hemodynamics study.

### Study Design

During the first visit, all patients underwent pulmonary function testing, including determination of the reversibility of airflow obstruction in response to 20 µg of inhaled procaterol hydrochloride and analysis of arterial blood gas while breathing room air. They then performed a 6MD test while breathing compressed air and oxygen administered at 2 L/min via a random, double-blind, crossover design. The pulmonary hemodynamics study of the 43 patients who had given permission was performed on another day. The pulmonary hemodynamics study at rest and during constant workload exercise was administered while the subjects were breathing compressed air or oxygen supplied at 2 L/min in a random order.

### Table 1—Results of Pulmonary Function Tests and Arterial Blood Gas Analysis for Three COPD Patient Groups Classified in Accordance With the Severity of Airflow Obstruction (n = 75)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild, %FEV₁ &gt; 50%</th>
<th>Moderate, %FEV₁ &gt; 35% to ≤ 50%</th>
<th>Severe, %FEV₁ ≤ 35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>16</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Age, yr</td>
<td>71 ± 2</td>
<td>69 ± 1</td>
<td>66 ± 1</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.39 ± 0.06</td>
<td>0.95 ± 0.03†</td>
<td>0.61 ± 0.02‡†</td>
</tr>
<tr>
<td>%FEV₁</td>
<td>62.7 ± 2.9</td>
<td>40.9 ± 1.0†</td>
<td>25.0 ± 1.11‡†</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>47.0 ± 1.8</td>
<td>35.8 ± 0.9†</td>
<td>30.2 ± 1.21‡</td>
</tr>
<tr>
<td>Airtrapping, L</td>
<td>0.23 ± 0.06</td>
<td>0.36 ± 0.05</td>
<td>0.48 ± 0.06§</td>
</tr>
<tr>
<td>VC, % predicted</td>
<td>100.0 ± 3.0</td>
<td>93.1 ± 2.6</td>
<td>77.5 ± 2.11‡‡</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>211.3 ± 13.4</td>
<td>263.3 ± 17.0†</td>
<td>309.7 ± 11.3§‡‡</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>54.2 ± 1.2</td>
<td>60.4 ± 1.6†</td>
<td>69.2 ± 1.01‡</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>65.7 ± 2.5</td>
<td>48.0 ± 4.1†</td>
<td>50.0 ± 3.5‡</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>75.7 ± 1.9</td>
<td>68.6 ± 0.9†</td>
<td>70.6 ± 1.0†</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>39.6 ± 0.8</td>
<td>41.7 ± 0.5</td>
<td>42.7 ± 1.0†</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM, unless otherwise indicated. RV = residual volume; DLCO = diffusing capacity of the lung for carbon monoxide; TLC = total lung capacity.
†p < 0.05 vs mild group.
‡p < 0.05 vs moderate group.
All patients performed three 6MD tests with a rest of at least 20 min between each walk. A baseline walk was performed while the subjects were breathing room air, and the next two walks while they were breathing compressed air or oxygen supplied in a random order. Patients were tested while breathing either compressed air from a small portable 2.5-kg cylinder or oxygen from an identical cylinder; both gases were administered at 2 L/min via nasal cannulae. An assistant technician carried the portable cylinders during the walking tests. Pulse oximetric saturation (SpO₂) was monitored throughout the walk by using a SpO₂ monitor (Pulsox-8; Teijin; Osaka, Japan), and the lowest SpO₂ was recorded. Patients were blinded as to whether they were breathing oxygen or air. The test result consisted of the distance the patient could walk in 6 min along a measured corridor. Patients were allowed to rest when necessary, but were encouraged to complete as many lengths of the corridor as possible. The 6MD was evaluated from the percentage of the predicted value.¹⁴

Pulmonary Hemodynamic Study

A 7F Swan-Ganz thermodilution catheter (Becton Dickinson; Sandy, UT) was inserted through an antecubital vein or an internal neck vein into the pulmonary artery for measurements of pulmonary artery pressure (Ppa), pulmonary artery occlusion pressure (Pop), right atrial pressure, and cardiac output. A thin silicon tube was inserted into a brachial artery to measure systemic artery pressure and to obtain heparinized arterial blood. Ppa, right atrial pressure, and systemic artery pressure were monitored continuously by means of a disposable transducer system (SK-590; Nihon Koden; Tokyo, Japan) and registered on a recording device (WT-685G; Nihon Koden). The zero pressure point was referenced to the midthoracic level, and calibration was performed with a mercury manometer. Pop was measured with the balloon occlusion technique, and the result was accepted as satisfactory if the following criteria were met: (1) a marked drop in pressure when the balloon was inflated, and (2) a change in flow pattern from pulmonary artery to atrial pulse. Vascular pressures were electrically averaged, and the end-expiratory levels were measured over three to four respiratory cycles. The intravascular pressures shown herein are expressed as mean pressures. Cardiac output was measured with the thermodilution method using a computer (Edwards model 9520 CO₂; Edwards Laboratory; Santa Ana, CA). Cardiac output values were measured in triplicate and averaged, the cardiac index (CI) was calculated as cardiac output/body surface area, the heart rate was monitored by ECG, and pulmonary vascular resistance indexes (PVRIs) were calculated as (Ppa – Pop)/CI.

As a warm-up before the examination, the patients were kept in the supine position while breathing compressed air at 2 L/min through a facemask for at least 30 min. The exercise was performed on an electrically braked bicycle ergometer (Reclining Ergometer model WLP-300 ST; Lode BV; Groningen, The Netherlands) with a constant workload of 25 W. Before the start of the exercise, the patient rested for a few minutes with his feet placed up on the bicycle ergometer (with the legs at a 0° to 30° angle to the horizontal) for baseline measurements. Pulmonary hemodynamics and arterial blood sampling during exercise were measured when a steady state had been attained as judged by minute-to-minute oxygen consumption measured with a Metabolic Measurement Cart/System (Model 2000; SensorMedics; Yorba Linda, CA). The measurements were usually performed 3 min after the start of the exercise. During each experiment, the peripheral oxygen saturation of all patients was monitored continuously with an SpO₂ monitor (Pulsox-8; Teijin).

Statistical Analysis

The data herein are shown as mean ± SEM. Variables for breathing compressed air and oxygen were compared by means of the Student paired t test. When the data for the variables showed a normal distribution in the groups, the comparison among the groups was performed with a one-way analysis of variance, followed by multiple comparisons using the Tukey-Kramer method. When the data for the variables did not show a normal distribution, they were compared by using the Kruskal-Wallis test, after which multiple comparisons among groups were performed with the nonparametric Tukey-Kramer method. The correlation between variables was examined by calculating the Pearson product correlation coefficient. A value of p < 0.05 was considered significant.

RESULTS

Effects of Oxygen Inhalation on 6MD

Although there was no difference in the lowest SpO₂ levels among the three groups, 6MD results while subjects were breathing compressed air showed a significant decrease in accordance with the severity of airflow obstruction (Table 2), and showed a significant positive correlation with %FEV₁ (r = 0.60, p < 0.01). However, 6MD did not show any correlation with PaO₂ at rest (r = 0.19) or with minimum SpO₂ during the walking test (r = 0.07) in conjunction with the breathing of compressed air. Oxygen inhalation resulted in a significant increase in 6MD results for all groups, which was higher in accordance with the severity of airflow obstruction, and was significantly higher for the moderate-to-severe groups than for the mild group. The rate of increase in 6MD results showed a weak, but significant, negative correlation with %FEV₁ (Fig 1), but no correlation with either PaO₂ at rest (r = 0.04) or the minimum SpO₂ recorded during the walking test with the breathing of compressed air (r = 0.03). The patients in each severity group were then classified into two subgroups, one subgroup with a reduction in SpO₂ to ≤ 88% during the walking test (severe desaturation subgroup), and one subgroup with a SpO₂ reduction not to reach < 88% (mild desaturation subgroup) while breathing compressed air. It was found that the supplemental oxygen produced a significant increase in the 6MD for the patients of each subgroup except for patients with mild desaturation and mild airflow obstruction. The effect of oxygen on 6MD results tended to be higher for the severe than for the mild desaturation subgroup in each severity group, but there were no significant differences (Fig 2). The effect of oxygen on 6MD was also greater in both subgroups in accordance with the severity of airflow obstruction.

Effects of Oxygen Inhalation on Pulmonary Hemodynamics During Exercise

There was no significant difference among the three groups in terms of pulmonary hemodynamics.
at rest while breathing either compressed air or oxygen (Table 3). The exercise induced significant increases in the Ppa, Pop, and CI of all groups while the patients were breathing either compressed air or oxygen. PVRI also significantly increased during exercise in the severe group, with the rates of increase in Ppa and Pop of the severe group being significantly higher than in those of the mild-to-moderate groups. Oxygen inhalation did not cause any change in the CI at rest or during exercise in any group. However, during exercise in the moderate-to-severe groups, oxygen inhalation significantly reduced the increase in Ppa and Pop, and completely inhibited the increase in PVRI. Classifying the patients into two groups (reduction in PaO2 to ≤55 mm Hg during exercise while breathing compressed air and the PaO2 level remaining at >55 mm Hg) revealed that the oxygen inhalation significantly reduced the increases in Ppa and Pop in both groups. However, there was no difference in these effects of oxygen between the two groups (Fig 3), nor was there any correlation with PaO2 at rest (Ppa, r = 0.04; Pop, r = 0.06) or the maximum reduction in PaO2 during exercise while breathing compressed air (Ppa, r = 0.001; Pop, r = 0.04). However, the decrease in Pop during exercise with oxygen significantly and positively correlated with the airtrapping index (vital capacity [VC] – FVC) [Fig 4].

**Table 2—Results of a 6MD Test Performed by Patients With COPD While Breathing Compressed Air and Oxygen at 2 L/min for Three Patient Groups Classified According to the Severity of Airflow Obstruction (n = 75)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild, %FEV1 &gt; 50%</th>
<th>Moderate, %FEV1 &gt; 35% to ≤50%</th>
<th>Severe, %FEV1 ≤35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compressed Air</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MD, m</td>
<td>475 ± 20</td>
<td>366 ± 20†</td>
<td>310 ± 22†</td>
</tr>
<tr>
<td>6MD, % predicted</td>
<td>92.9 ± 5.0</td>
<td>70.5 ± 4.7†</td>
<td>56.7 ± 4.1†</td>
</tr>
<tr>
<td>Minimum SpO2</td>
<td>85.6 ± 2.0</td>
<td>84.3 ± 1.3</td>
<td>82.5 ± 1.4</td>
</tr>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MD, m</td>
<td>487 ± 20§</td>
<td>390 ± 17†§</td>
<td>342 ± 19†§</td>
</tr>
<tr>
<td>6MD, % predicted</td>
<td>95.4 ± 5.4§</td>
<td>75.3 ± 4.2‡</td>
<td>62.4 ± 3.6†§</td>
</tr>
<tr>
<td>Minimum SpO2</td>
<td>89.5 ± 1.7§</td>
<td>88.8 ± 1.1§</td>
<td>88.9 ± 0.9§</td>
</tr>
<tr>
<td>% increase in 6MD by O2</td>
<td>2.6 ± 0.8</td>
<td>9.7 ± 3.4†</td>
<td>20.2 ± 6.3§</td>
</tr>
</tbody>
</table>

*Values are mean ± SEM.
†p < 0.05 vs mild group.
‡p < 0.05 vs moderate group.
§p < 0.05 vs compressed air.

**Discussion**

Certain benefits of oxygen inhalation during exercise for some patients with COPD and mild hypox-
emia at rest have been reported.10–13 However, it is difficult to predict in which patients oxygen inhalation will be effective or more prominent than in others.10,12 Woodcock et al.10 demonstrated that oxygen inhalation resulted in an increase in the 6 MD by 12% and improved dyspnea by 16% in pink puffer patients. However, there was no significant correlation between the degree of these improvements and the findings from pulmonary function tests or arterial blood gas analysis at rest. Our study, however, demonstrated that oxygen inhalation significantly increased the exercise performance of patients with COPD who showed mild hypoxemia at rest. The improvement in exercise performance with oxygen

<table>
<thead>
<tr>
<th>Variables</th>
<th>Air</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ppa, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>21.5 ± 2.7</td>
<td>20.1 ± 2.7</td>
</tr>
<tr>
<td>Exercise</td>
<td>32.7 ± 3.2†</td>
<td>32.0 ± 3.2†</td>
</tr>
<tr>
<td>Pop, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>9.3 ± 1.0</td>
<td>7.8 ± 1.4</td>
</tr>
<tr>
<td>Exercise</td>
<td>13.8 ± 1.2†</td>
<td>13.4 ± 2.7†</td>
</tr>
<tr>
<td>CI, L/mm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>3.40 ± 0.25</td>
<td>3.26 ± 0.37</td>
</tr>
<tr>
<td>Exercise</td>
<td>5.35 ± 0.36†</td>
<td>4.89 ± 0.38†</td>
</tr>
<tr>
<td>PVRI, mm Hg/L/min/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>3.55 ± 0.46</td>
<td>3.91 ± 0.65</td>
</tr>
<tr>
<td>Exercise</td>
<td>3.48 ± 0.41</td>
<td>3.44 ± 0.50</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>72.7 ± 3.7</td>
<td>144.6 ± 12.4†</td>
</tr>
<tr>
<td>Exercise</td>
<td>59.6 ± 6.2†</td>
<td>86.8 ± 12.2†</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>35.8 ± 1.2</td>
<td>38.9 ± 1.8</td>
</tr>
<tr>
<td>Exercise</td>
<td>37.7 ± 2.0</td>
<td>39.3 ± 2.0</td>
</tr>
</tbody>
</table>

*Values are mean ± SEM. The intravascular pressures are mean pressures.
†p < 0.05 vs at rest.
‡p < 0.05 vs compressed air.
§p < 0.05 vs mild group.
||p < 0.05 vs both mild and moderate groups.
was more prominent in the moderate-to-severe groups than in the mild group, and correlated negatively with \%FEV$_1$, but was not associated with PaO$_2$ at rest or the degree of desaturation during the walking test. It has been demonstrated that supplemental oxygen results in acute improvements in exercise tolerance and breathlessness in patients with COPD who show exercise hypoxemia, but this phenomenon has not been sufficiently examined in patients without exercise hypoxemia. When the patients in our study were classified into two subgroups—severe and mild desaturation on exercise—for each of the airflow obstruction severity groups, the supplemental oxygen was found to have produced a significant increase in the 6MD performance in the patients of each subgroup except for those with mild desaturation and mild airflow obstruction. The effect of oxygen on 6MD results for the severe desaturation subgroup tended to be higher than on those for the mild desaturation subgroup in each severity group, although the differences were not significant. The effect of oxygen on exercise performance, moreover, was greater in line with the severity of airflow obstruction in both subgroups. These findings suggest that oxygen inhalation results in greater improvement in exercise performance by patients with COPD showing severe airflow obstruction, even though these patients may show mild hypoxemia at rest or during exercise.

It has been suggested that the mechanisms leading to improvement in exercise tolerance as a result of supplemental oxygen are multifactorial. These factors include relief of dyspnea, prevention of desaturation during exercise, improvement in pulmonary hemodynamics, reduction of ventilation and associated dynamic hyperinflation, and improved oxygen delivery and oxidative metabolism in respiratory and peripheral muscles during exercise. As for the related mechanisms, it has been suggested that the relief of dyspnea and improved exercise tolerance with oxygen can be primarily explained by a reduction in ventilation and associated dynamic hyperinflation, especially in patients who are relatively normoxic at rest. Somfay et al. recently demonstrated that supplemental oxygen significantly reduces dyspnea scores, dynamic hyperinflation assessed from inspiratory capacity maneuver results, ventilation, and respiratory frequency during exercise in nonhypoxic patients with severe COPD. This improvement in exercise capacity was found to correlate with the reduction in dynamic hyperinflation. Dynamic hyperinflation, which readily develops in patients with COPD with severe airflow obstruction and hyperinflation, has a deleterious mechanical effect on the respiratory muscles, contributes to a sensation of breathlessness, and limits exercise ca-

pace. It is therefore not surprising that the effect of oxygen was most prominent in patients with severe airflow obstruction. This suggests that the improvement in exercise capacity and dyspnea is a result of supplying oxygen for patients with severe airflow obstruction, and that mild hypoxemia may be primarily related to reduced dynamic hyperinflation caused by the decrease in augmented ventilation during exercise.

A greater rise in Ppa and Pop occurs during exercise in patients with COPD than in normal subjects. In our study, both Ppa and Pop of all groups significantly increased during exercise, and these increases were most prominent in patients with severe airflow obstruction. Several mechanisms underlying the elevation of Ppa and Pop during exercise have been proposed, including hypoxic pulmonary vasoconstriction, reduction of the capillary bed because of lung destruction, vascular remodeling, and extramural compression caused by increased alveolar pressure. It has also been suggested that the elevation of Pop may be related mainly to dynamic hyperinflation. Butler et al. reported that the increased Pop in patients with COPD during exercise was partly due to an increase in pressure in the cardiac fossa associated with lower-lobe gas trapping, because tachypnea alone, at the rate observed during exercise, produced an increase in the functional residual capacity and the volume in the lower-lobe area, leading to an increase in Pop. Furthermore, we have demonstrated that the improvement in lung hyperinflation and airflow obstruction after lung volume reduction surgery resulted in a reduced increase in Pop during exercise, whereas the increase in Ppa during exercise did not change in cases of severe emphysema. These findings suggest that the development of dynamic hyperinflation followed by an increase in ventilation may contribute to the development of pulmonary hypertension during exercise.

Oxygen inhalation did not change the level of Ppa or Pop at rest in any group, but significantly reduced not only the increase in Ppa, but also that in Pop induced by exercise in moderate-to-severe COPD. The effect of oxygen on pulmonary hemodynamics was not due to the decrease in cardiac output because the increase in cardiac output induced by exercise did not change with oxygen inhalation. There are several reasons for the decrease in Ppa during exercise with oxygen. First, the relief of hypoxic pulmonary vasoconstriction with oxygen must have contributed to the decrease in Ppa during exercise because it almost completely prevented the increase in PVRI induced by exercise in moderate-to-severe COPD. Second, the reduction in Pop as a result of oxygen inhalation contributed to the de-
crease in Ppa in moderate-to-severe COPD. The precise reason why the increase in Ppa caused by exercise was reduced by oxygen is not clear. However, the fact that supplemental oxygen reduces dynamic hyperinflation as shown by Somfay et al., and that the decrease in Ppa during exercise with oxygen significantly and positively correlated with the airtrapping index (VC/O2), suggests that the decrease in dynamic hyperinflation due to the suppression of ventilation by oxygen may have resulted in the reduction in Ppa.

In conclusion, oxygen inhalation during exercise significantly improved exercise performance in patients with COPD with mild hypoxemia. The degree of improvement in exercise performance correlated with the severity of airflow obstruction, but was not associated with rest or exercise hypoxemia. Oxygen inhalation also improved pulmonary hypertension in patients with moderate to severe airflow obstruction, and this effect was found to be the result of the inhibition of hypoxic vasoconstriction and the reduction in Ppa, which positively correlated with the airtrapping index. These findings suggest that supplemental oxygen is beneficial for patients with moderate-to-severe COPD. The structure and pulmonary hypertension during exercise even though their hypoxemia is mild at rest and during exercise. Further, the effects of oxygen may be primarily associated with a decrease in dynamic hyperinflation caused by the decrease in augmented ventilation during exercise.

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