Exercise Capacity Deterioration in Patients With COPD

Longitudinal Evaluation Over 5 Years

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**Background:** Although exercise capacity is an important outcome measure in patients with COPD, its longitudinal course has not been analyzed in comparison to the change in pulmonary function.

**Purpose:** To examine how exercise capacity would deteriorate over time in patients with COPD, and what factors would contribute to it.

**Methods:** A total of 137 male outpatients with moderate-to-very-severe COPD were examined. The average age was 69.0 ± 6.6 years (± SD), and the mean postbronchodilator FEV1 was 45.9 ± 15.4% predicted. Progressive cycle ergometry and pulmonary function testing were performed at entry, and every 6 months thereafter over 5 years. Due to the presence of missing data, a mixed-effect model analysis was then used to estimate the longitudinal changes in various clinical parameters.

**Results:** Peak oxygen uptake (\( \dot{V}O_2 \)), peak minute ventilation (\( \dot{V}E \)), and peak tidal volume (\( V_T \)) during exercise declined significantly over time (\( p < 0.0001 \)), which was no less rapid than the deterioration in FEV1. The mean decline rates for peak \( \dot{V}O_2 \) were 32 ± 60 mL/min/yr and 0.5 ± 1.0 mL/min/kg/yr. Multiple regression analysis revealed that the changes in peak \( \dot{V}E \), peak \( V_T \), and peak respiratory rates were significant predictors for the change in peak \( \dot{V}O_2 \).

**Conclusion:** We demonstrated clear evidence of measurable and progressive deterioration in exercise capacity in COPD patients, which was no less rapid than the decline in airflow limitation. Dynamic ventilatory constraints during exercise also deteriorated over time, which most significantly contributed to this exercise capacity deterioration. In addition to pulmonary function, the longitudinal follow-up of exercise capacity is important not to miss the overall deterioration in COPD.

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**Key words:** airflow limitation; COPD; dynamic ventilatory constraint; exercise capacity; longitudinal study; progressive cycle ergometry

**Abbreviations:** BMI = body mass index; DLco = diffusing capacity for carbon monoxide; HR = heart rate; IC = inspiratory capacity; RV = residual volume; SaO2 = arterial oxygen saturation; VCO2 = carbon dioxide production; \( \dot{V}E \) = minute ventilation; \( \dot{V}O_2 \) = oxygen uptake; \( V_T \) = tidal volume; 6MWD = 6-min walking distance

COPD is characterized by the presence of airflow limitation that is not fully reversible and is usually progressive. Therefore, the change in disease progression is often expressed as the rate of decline in FEV1, and its longitudinal change has been interpreted as the natural history of COPD. However, COPD has other extrapulmonary features and should be regarded as a systemic disorder. No measure of any one aspect of COPD such as pulmonary function can adequately capture the overall effect of this disease. Therefore, to multidimensionally investigate how various parameters except for FEV1 can change during the course of COPD is essential in understanding the overall clinical deterioration in COPD.

Exercise capacity has become an important outcome measure in COPD, as many patients complain of exercise intolerance and exertional dyspnea, and because it is a major determinant of an impaired health status. The improvement of exercise capacity is listed as one of the major goals for the manage-
ment of COPD. Since no resting physiologic measurements can predict exercise capacity, performing direct cardiopulmonary exercise testing is recommended, which can provide useful information that is not available from other resting measurements. Furthermore, the significance of exercise capacity has been emphasized recently from the viewpoint of predicting mortality in COPD. However, there are no studies investigating how exercise intolerance in COPD will progress over time.

In analyzing longitudinal data, the presence of missing data due to nonattendance or dropping out is a problem. Some methods dealing with it are proposed because the exclusion of dropouts causes underevaluation of the results.

We hypothesized that the long-term deterioration in exercise capacity could be detectable in patients with COPD and that it would be less related with the decline in pulmonary function. Therefore, we performed pulmonary function and exercise testing, using progressive cycle ergometry, in patients with COPD regularly over 5 years, because laboratory cardiopulmonary exercise testing includes more information by measuring physiologic and perceptual responses to exercise than field tests. Then we compared its change with that of pulmonary function, and analyzed which factors contributed to the long-term deterioration in exercise capacity in patients with COPD.

Materials and Methods

Subjects

We recruited 137 consecutive male outpatients with moderate-to-very-severe COPD, as defined by the American Thoracic Society and European Respiratory Society 2004 guidelines. These participants consisted of 131 patients enrolled in a previous study investigating the relationship between the baseline measures and 5-year mortality between September 1995 and January 1997, and 6 patients who were added from February 1997 to April 1997. The entry criteria included the following: (1) a smoking history of > 20 pack-years; (2) maximal FEV1/FVC ratio < 0.7 and postbronchodilator FEV1 < 80% of predicted normal; (3) regular attendance at the Kyoto University Hospital > 6 months; (4) no exacerbations in the preceding 6 weeks; and (5) no uncontrolled comorbidities. The clinical measurements were evaluated on the same day. Body mass index (BMI) was calculated by dividing the patient’s weight in kilograms by their height (meters) squared. This study was performed as part of our standard outpatient treatment and care.

Outcome Measures

Pulmonary function tests were performed at least 12 h after the withdrawal of inhaled bronchodilators. Based on the recommended method, the subjects underwent spirometry using a spirometer (Autospiro AS-600; Minato Medical Science; Osaka, Japan) before and at 15 min and 60 min after inhaling salbutamol (400 µg) and ipratropium bromide (80 µg) using a metered-dose inhaler with a spacer device (InspirEase; Schering-Plough; Osaka, Japan). Spirometry was performed three times, and the largest values were analyzed. The residual volume (RV) was measured by the closed-circuit helium method, and the diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath technique (CHESTAC-65V; Chest; Tokyo, Japan). The predicted values were those established by the Japan Society of Chest Diseases.

Exercise tests were performed 60 min after the inhalation of bronchodilators using symptom-limited progressive cycle ergometry as described in detail elsewhere. Briefly, the patients wore a facemask and began unloaded pedaling for 3 min, after which the workload was increased progressively by increments of 1 W every 3 s to the limit of tolerance. The exercise data were recorded using an automated exercise testing system that converts the breath-by-breath analog input into a digital form on-line. Minute ventilation (Ve) and oxygen tension in the expired air were determined every eight breaths, and mean Ve, oxygen uptake (V̇O2), and carbon dioxide production (V̇CO2) were then calculated. Their peak values were the highest levels reached during exercise. Arterial oxygen saturation (SaO2) was measured through pulse oximetry, and heart rate (HR) was recorded using ECG. At the end of the exercise, symptoms of breathlessness were scored with the Borg scale (0 to 10).

Longitudinal Study

Eligible COPD patients who had been managed > 6 months had their clinical measures evaluated at entry, and every 6 months thereafter over a 5-year period. On each reevaluation day, each subject was confirmed to meet the definition of COPD. When an exacerbation of COPD requiring a change in the treatment occurred within 4 weeks of a reassessment day, the evaluation was postponed for at least 4 weeks until the patient recovered.

Follow-up Data

Among the 137 COPD patients enrolled, 67 patients performed the last 5-year exercise evaluation, and only 1 patient was unavailable for follow-up. Twenty-five patients died during the 5 years, and 36 patients dropped out due to the inability to attend the hospital evaluations. Five patients could not perform exercise tests due to severe disabilities. Three patients skipped the last attendance.

Statistical Analysis

The results are expressed as mean ± SD, unless otherwise stated. Mixed-effect models were used to estimate the longitudinal changes in clinical parameters using software (Proc Mixed; SAS Institute; Cary, NC). In these analyses, the covariates included age and smoking status as fixed effects, whereas time was entered as a random effect. By performing these analyses, all data from 137 patients with COPD were included. Simple regression analyses were performed to investigate whether the changes in clinical variables would predict the change in peak V̇O2. Then, stepwise multiple regression analyses were used to identify those variables that could best predict the change in peak V̇O2. In these analyses, the variables whose changes significantly predicted the change in peak V̇O2 in simple regression analyses were used as explanatory variables. Furthermore, simple regression analyses were performed to investigate whether the baseline measurements would predict the change in peak V̇O2; p < 0.05 was considered statistically significant.
The baseline characteristics of the 137 male patients are shown in Table 1. Their average age was 69.0 ± 6.6 years, and postbronchodilator FEV1 was 45.9 ± 15.4% predicted. When the patients were classified according to their COPD severity based on postbronchodilator FEV1, 53 patients (39%) had moderate COPD (FEV1 ≥ 50 to < 80% predicted), 59 patients (43%) had severe COPD (FEV1 ≥ 30 to < 50% predicted), and 25 patients (18%) had very severe COPD (FEV1 < 30% predicted).

Changes in peak VO2, peak VE, and peak tidal volume (VT) during exercise and postbronchodilator FEV1 are shown in Figure 1 in 54 patients with COPD who had complete data sets with no missing data every 6 months over 5 years. These results compare individual changes in each measurement. The declines in those exercise indexes were more prominent than the change in postbronchodilator FEV1.

The annual changes in the clinical measurements are shown in Table 2. BMI decreased significantly (p = 0.0013). Prebronchodilator and postbronchodilator FEV1 values declined significantly in patients with moderate-to-very-severe COPD at mean rates of 11.8 mL/yr (p = 0.027) and 25.4 mL/yr (p < 0.0001), respectively. Regarding the outcomes of the exercise testing, peak VO2 deteriorated significantly at mean rates of 32 mL/min/yr and 0.5 mL/min/kg/yr (p < 0.0001). Peak VO2, peak VE, and peak VT also deteriorated significantly over time (p < 0.0001). Although peak respiratory rates did not change significantly, peak HR decreased at a mean rate of 1.6 beats/min/yr.

Simple regression analyses were performed to investigate whether the changes in clinical variables would predict the change in peak VO2 (mL/min/kg/yr) [Table 3]. It was best explained by the change in peak VE (coefficient of determination [r2] = 0.69, p < 0.0001). It was also significantly explained by the changes in peak VT (r2 = 0.31, p < 0.0001), peak respiratory rate (r2 = 0.19, p < 0.0001), and peak HR (r2 = 0.23, p < 0.0001). The change in peak VO2 was weakly significantly explained with the change in postbronchodilator FEV1. Figure 2 shows the relationships between the change in peak VO2 and the change in postbronchodilator FEV1 and between the change in peak VO2 and the change in peak VE. The figure indicates a more significant relationship for the change in peak VO2 with the change in peak VE than with the change in FEV1.

Stepwise multiple regression analyses were performed to identify the variables that could best predict the change in peak VO2 (Table 4).17 The change in peak VE most significantly accounted for 49% of the variance. The changes in peak VT and peak respiratory rate also significantly accounted for 17% and 7% of the variance, respectively.

Simple regression analyses were performed to investigate whether the clinical measurements at baseline would predict the change in peak VO2. However, no static pulmonary function measures (FEV1, total lung capacity, RV, functional residual capacity, DLCO, DLCO/alveolar volume) significantly predicted the change in peak VO2 ( r2 < 0.01, p > 0.05), nor did baseline exercise indexes (peak VO2, peak VE, peak VT) [ r2 < 0.01, p > 0.05].

**DISCUSSION**

We found clear evidence of a measurable and progressive deterioration in exercise capacity in patients with moderate-to-very-severe COPD. To our knowledge, this is the first published study on COPD to demonstrate a longitudinal decline in laboratory exercise capacity evaluated by peak VO2 on progressive cycle ergometry prospectively over 5 years. We previously reported that peak VO2 was the most significant predictor of mortality among several in-

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**Table 1—Baseline Characteristics of 137 Male Patients With COPD**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD or No.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>69.0 ± 6.6</td>
<td>48–89</td>
</tr>
<tr>
<td>Former/current smokers</td>
<td>103/34</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>21.2 ± 3.0</td>
<td>14.0–29.0</td>
</tr>
<tr>
<td>Pulmonary function testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebronchodilator FEV1, L</td>
<td>0.98 ± 0.38</td>
<td>0.36–2.15</td>
</tr>
<tr>
<td>Prebronchodilator FEV1, % predicted</td>
<td>36.7 ± 14.0</td>
<td>14.7–73.8</td>
</tr>
<tr>
<td>Postbronchodilator FEV1, L</td>
<td>1.22 ± 0.41</td>
<td>0.37–2.19</td>
</tr>
<tr>
<td>Postbronchodilator FEV1, % predicted</td>
<td>45.9 ± 15.4</td>
<td>15.3–80.0</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>103.1 ± 15.2</td>
<td>60.7–143.4</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>143.5 ± 42.3</td>
<td>56.7–268.7</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>110.0 ± 25.3</td>
<td>49.0–192.1</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>646 ± 21.0</td>
<td>227.1312</td>
</tr>
<tr>
<td>DLCO/VA, mL/min/L/mm Hg</td>
<td>3.42 ± 1.20</td>
<td>1.12–7.11</td>
</tr>
<tr>
<td>Exercise testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO2, mL/min</td>
<td>830 ± 257</td>
<td>292–1,603</td>
</tr>
<tr>
<td>Peak VO2, mL/min/kg</td>
<td>14.8 ± 3.8</td>
<td>4.5–24.3</td>
</tr>
<tr>
<td>Peak VO2, mL/min</td>
<td>905 ± 328</td>
<td>201–1,919</td>
</tr>
<tr>
<td>Peak VE, L/min</td>
<td>40 ± 11</td>
<td>10–68</td>
</tr>
<tr>
<td>Peak VT, mL</td>
<td>1,358 ± 323</td>
<td>633–2,271</td>
</tr>
<tr>
<td>Peak Vt, % predicted vital capacity</td>
<td>37.5 ± 8.3</td>
<td>19.4–59.5</td>
</tr>
<tr>
<td>Peak respiratory rate, breaths/min</td>
<td>30 ± 6</td>
<td>17–49</td>
</tr>
<tr>
<td>Lowest SaO2, %</td>
<td>91 ± 5</td>
<td>78–99</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>124 ± 19</td>
<td>81–172</td>
</tr>
<tr>
<td>Peak dyspnea, Borg score</td>
<td>6.4 ± 1.5</td>
<td>3–10</td>
</tr>
</tbody>
</table>

*FRC = functional residual capacity; TLC = total lung capacity; VA = alveolar volume.*
dexes evaluating COPD, and we could also detect this significant longitudinal deterioration in COPD in the present study. We also found out that the dynamic ventilatory constraints also progressed over time in COPD, which contributed most significantly to the longitudinal decline in exercise capacity.

Furthermore, the present study indicates the decline in peak VO$_2$ was more rapid than the decline in FEV$_1$ in patients with COPD as shown in Figure 1. Exercise capacity is affected by not only pulmonary function but also by other comprehensive factors such as ventilatory limitation, gas exchange, muscular function, and cardiovascular limitation. In addition, the change in peak VO$_2$ was only weakly correlated with the change in FEV$_1$. Therefore, an evaluation of FEV$_1$ only in the management of COPD patients might lead to overlooking the overall deterioration in COPD, and performing cardiopulmonary exercise testing would be helpful in recognizing it.

The present study did not include the control group as one limitation. According to the most widely used set of reference values by Jones et al., there is a mean difference of 21 mL/min of peak VO$_2$ by 1 year. It means that the mean annual decline rate of 32 mL/min of peak VO$_2$ in this study is higher, although a direct comparison may be difficult. In addition, this annual decline rate may be relatively high as compared to the mean lowered baseline value of 826 mL/min in patients with COPD. Furthermore, considering that this occurs in spite of pharmacologic treatments for COPD patients to improve symptoms or clinical parameters including exercise capacity, that decline cannot be neglected.

Another novel finding was that dynamic ventilatory constraints progressed significantly over time. Although expiratory airflow limitation has been the most obvious physiologic manifestation of COPD, due to reduced lung recoil as well as intrinsic airway narrowing, a restrictive ventilatory deficit due to

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**Figure 1.** Changes in peak VO$_2$ (top left, A), peak VE (top right, B), and peak VT standardized as percentage of predicted vital capacity (bottom left, C) during exercise and postbronchodilator FEV$_1$ (bottom right, D) in 54 patients with COPD who had complete data sets with no missing data every 6 months over 5 years. Values are expressed as mean ± SE.
dynamic lung hyperinflation is the most important mechanical consequence of this. The sense of unsatisfied inspiration, which is the dominant qualitative descriptor of exertional dyspnea in COPD patients, is considered to be due to the inability to expand their Vt in the face of increased inspiratory effort during exercise. In a cross-sectional study, O'Donnell et al reported that the peak V\textsuperscript{\textcircled{O}2} during exercise emerged as the strongest contributory variable to peak V\textsuperscript{\textcircled{O}2}. Such possible mechanistic relationships between dynamic ventilatory constraints, dynamic hyperinflation, exercise intolerance, and exertional dyspnea have been often reported.

The worsening of dynamic volume constraints leads to a compensatory increase in the respiratory rate of COPD patients, and then oppositely to the worsening of dynamic hyperinflation, which results in a deterioration of exertional dyspnea and breathing patterns. This vicious cycle might cause an impairment of health status in patients with COPD.

Exercise intolerance is multifocal in COPD; in cross-sectional studies, some contributing factors are recognized: (1) ventilatory limitation; (2) peripheral muscle dysfunction; (3) nutritional status; (4) cardiac limitation; and (5) gas exchange abnormalities. Then, symptoms of dyspnea, fatigue, or muscle weakness caused through these or combined factors limit exercise performance in COPD patients. Although insufficient indexes were measured to evaluate exercise limitation in detail in the present study, it would be meaningful to analyze exercise limitation from a longitudinal point of view. Multiple regression analyses revealed that the deterioration in ventilatory-related factors such as peak Vt, peak V\textsuperscript{\textcircled{O}2}, peak respiratory rate, which was due to impaired respiratory mechanics or ventilatory muscle dysfunction, played the most important role in determining longitudinal exercise intolerance. Although BMI, lowest Sao\textsubscript{2}, and peak HR significantly declined over time, and the latter two were important factors in simple regression analyses, they were not statistically significant in multiple regression analyses. Therefore, the worsening of nutritional status, gas abnormality, and cardiac impairment were considered to be weaker longitudinal exercise limiting factors than deteriorations in ventilatory-related factors.

We showed that neither static pulmonary function measures nor exercise indexes at baseline predicted the decline in exercise capacity. According to the cross-sectional study by O'Donnell et al, peak V\textsuperscript{\textcircled{O}2} significantly correlated with inspiratory capacity (IC) at peak exercise and IC at rest. Although we did not measure IC in the present study, neither index for static hyperinflation nor volume constraints during exercise at baseline predicted the subsequent decline in exercise capacity. The authors also reported that resting diffusing capacity significantly correlated with peak V\textsuperscript{\textcircled{O}2} on progressive cycle ergometry, and inversely with the rate of change in dynamic hyperinflation in patients with COPD. However, the present study demonstrated that resting diffusing capacity at baseline failed to predict the subsequent longitudinal decline in peak V\textsuperscript{\textcircled{O}2}. Therefore, our results indicate the importance of direct serial measurements of exercise capacity to understand its deterioration in COPD.

We used peak V\textsuperscript{\textcircled{O}2} on progressive cycle ergometry as an index of exercise capacity, although there is another widely used parameter, the 6-min walking distance (6MWD) on the 6-min walking test. Progressive cycle ergometry was chosen on the premise of two points: (1) we wanted to get more information on physiologic measurements from laboratory tests,
and (2) we were not sure whether 6MWD was a suitable index in evaluating longitudinal intraindividual comparisons because, as a limitation, such walking tests are highly dependent on patient motivation and are not controlled by the pace of walking during the test. However, strong relationships between peak VO\textsubscript{2} and 6MWD are reported in moderate-to-severe COPD,\textsuperscript{26,27} and 6MWD significantly predicted mortality\textsuperscript{7,8} as peak VO\textsubscript{2}.\textsuperscript{6} Although there are no "gold standards" in evaluating exercise capacity in patients with COPD, recognizing the characteristics of each exercise test is important in choosing an appropriate method.\textsuperscript{13,17,27–29}

In the present study, the mean changes in FEV\textsubscript{1} might be small, although they were statistically significant. First, we managed to determine the pharmacologic treatment to maintain pulmonary function using bronchodilators, inhaled corticosteroids, or low-dose oral corticosteroids during the 5-year period, although the present guideline\textsuperscript{1} does not recommend the use of systemic corticosteroids. Therefore, in comparison to the clinical trials designed to investigate the effects of inhaled corticosteroids on the rate of decline in FEV\textsubscript{1},\textsuperscript{30} the present study might underestimate the changes in FEV\textsubscript{1} as reported previously.\textsuperscript{31} Second, the present study population had moderate-to-very-severe COPD, and FEV\textsubscript{1} in some patients with severe COPD might have been too low to decrease any further. Rather, we have to pay attention to the result that exercise capacity decreased significantly even where the change in FEV\textsubscript{1} was small.

Approximately half of the patients dropped out of the study at 5 years. However, for example, in the Inhaled Steroids in Obstructive Lung Disease in Europe trial,\textsuperscript{30} among the 751 patients randomized, 349 patients (46.5\%) dropped out at 3 years. The present study also targeted moderate-to-very-severe COPD patients, the observational period was longer (5 years), and the study protocol included invasive exercise tests. Considering this, our dropout rate is

Table 4—Stepwise Multiple Regression Analysis Showing the Relative Contribution of Each Variable To Predict the Changes in Peak VO\textsubscript{2}

<table>
<thead>
<tr>
<th>Changes per Year</th>
<th>Coefficient</th>
<th>SE</th>
<th>R\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.330</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>Postbronchodilator FEV\textsubscript{1}, % predicted</td>
<td>0.184</td>
<td>0.028</td>
<td>0.49</td>
</tr>
<tr>
<td>Peak Ve, L/min</td>
<td>0.176</td>
<td>0.042</td>
<td>0.17</td>
</tr>
<tr>
<td>Peak V\textsubscript{t}, % predicted vital capacity</td>
<td>0.063</td>
<td>0.031</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak respiratory rate, breaths/min</td>
<td>0.063</td>
<td>0.031</td>
<td>0.07</td>
</tr>
<tr>
<td>Lowest Sa\textsubscript{O}2, %</td>
<td>0.063</td>
<td>0.031</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>0.063</td>
<td>0.031</td>
<td>0.07</td>
</tr>
<tr>
<td>Cumulative R\textsuperscript{2}</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}R\textsuperscript{2} indicates the coefficient of multiple determinations. Missing data indicate that explanatory variables were not statistically significant.
not necessarily high. Instead, to deal with missing values, we used mixed-effects models and estimated the slopes for analyzing longitudinal data. Since dropouts include missing at random and not missing at random, dropout reasons are complex.32 It is impossible that one model will be ideal for all analyses. However, when the data set has a lot of missing values, those models are reported to yield parameter estimates with less bias,33 as we previously discussed.34,35

The present study has some limitations. First, the sample size is small, male only, and from one university hospital. Therefore, any generalization of the results might be limited. Second, we did not include the number of exacerbations in the study protocol, since its importance was not discussed previously. However, the relationships between exacerbations and longitudinal changes in pulmonary function or health status have recently been discussed.31,36 Therefore, the effects of exacerbations on the long-term changes in exercise capacity should be studied in the future.

In conclusion, we demonstrated that exercise capacity deteriorated over time in patients with moderate-to-very-severe COPD, which was no less rapid than the decline in airflow limitation. In addition, progressive dynamic ventilatory constraints contributed strongly to the longitudinal deterioration in exercise capacity. Since exercise capacity deterioration was only weakly correlated with the decline in FEV₁ and would lead to a worsening of exertional dyspnea and health status in COPD patients, it should be followed with caution not to miss the overall deterioration in COPD.

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