Prediction of \( \text{PaO}_2 \) during Treadmill Walking in Patients with COPD*

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We studied the possibility of predicting \( \text{PaO}_2 \) during exercise of a given oxygen uptake (\( \text{Vo}_2 \)) from resting pulmonary function tests (PFTs) in patients with chronic obstructive pulmonary disease (COPD). The three-minute incremental treadmill exercise was performed with serial measurements of \( \text{PaO}_2 \) via intra-arterial catheter in 46 patients (mean \( \text{FEV}_1 = 1.09 \pm 0.49 \text{L}, \) mean \( \text{FEV}_1/\text{FVC} = 44 \pm 15 \) percent). In most of the patients, the changes of \( \text{PaO}_2 \) were quite linear in relation to the oxygen uptake, so a slope (\( \text{PaO}_2/\text{Vo}_2 \)) could be obtained from the regression equation in each patient. The mean value of the slope (SL) was \(-23.0 \pm 16.6 \) mm Hg/L \( \text{Vo}_2/\text{min} \). Correlation between SL and all parameters of resting PFTs were computed. Because of the high correlation coefficient between SL and \%Dco (SL = \(-59.3 + 0.501 \times \% \text{Dco}, r = 0.851, p < 0.001\)) it was possible to predict \( \text{PaO}_2 \) at a given \( \text{Vo}_2 \) using the following equation: \( \text{PaO}_2 = \text{PaO}_2 \) rest + SL\( \times (\text{Vo}_2 - 0.25) \), where SL was derived from measured \%Dco and resting \( \text{Vo}_2 \) was assumed 0.25 L/min. There was a high correlation between the predicted \( \text{PaO}_2 \) at \( \text{Vo}_2 \) of 1.0 L/min and the estimated \( \text{PaO}_2 \) obtained from individual \( \text{PaO}_2 \) regression with an r value = 0.898 and SEE = \pm 5.8 mm Hg. A prospective study in 12 patients with COPD was then carried out. There was a high correlation (r = 0.857) between the predicted \( \text{PaO}_2 \) obtained from the present equation and the estimated \( \text{PaO}_2 \) at \( \text{Vo}_2 = 1.0 \) L/min. It was concluded that \( \text{PaO}_2 \) during treadmill walking with a given oxygen uptake is predictable from a resting \( \text{PaO}_2 \) and a diffusing capacity. This predicted value may be useful in the management of patients with COPD.

In many patients with chronic obstructive pulmonary disease (COPD), considerable hypoxemia develops during exercise.\(^4\)\(^4\) It increases ventilatory requirement and right ventricular afterload leading to an early exercise limitation.\(^3\) Accordingly, for the management of patients with COPD, it is clinically important to predict the possible development of hypoxemia during exercise. Despite many previous studies concerning arterial \( \text{Po}_2 \) response during exercise in these patients, there are no reports on the quantitative prediction of hypoxemia in relation to workload from resting pulmonary function tests. By performing incremental treadmill exercise tests with serial arterial blood gas measurements in 46 patients with COPD, we observed linear changes of \( \text{PaO}_2 \) with increasing oxygen-uptake in most of the patients. From this observation, we tried to determine whether \( \text{PaO}_2 \) at a given workload could be predicted from resting pulmonary function tests. Although studies using noninvasive technique such as ear-oximeter\(^6\) or transcutaneous \( \text{O}_2 \) electrode\(^7\) have been reported, we used direct measurements in the present investigation.

**Materials and Methods**

**Subjects**

Forty-six patients with moderate to severe COPD were selected for the study. The diagnosis of COPD was made on the basis of clinical history, pulmonary function tests, and chest roentgenogram. They visited the First Department of Internal Medicine of Osaka City University Medical School between 1978 and 1984, and completed all pulmonary function and exercise tests. All patients were in a stable phase of their disease. Those with a history of right heart failure, \( \text{PaO}_2 \) at rest less than 60 mm Hg, and ischemic heart disease were excluded from the study. Patients were divided into two groups by the criteria including daily sputum production, chest roentgenogram, percent predicted TLC, and diffusing capacity.\(^4\) By these criteria, there were 28 patients with emphysematous type (group A) and 18 patients with bronchitic or intermediate type (group B). Anthropometric and pulmonary function data of the patients are listed in Table 1.

**Pulmonary Function and Exercise Tests**

Pulmonary function tests were performed within ten days prior to the exercise test. Spirometry was done with 13.5 L Benedict-Both spirometer connected to computerized calculator. Lung volumes were determined by the He dilution method and single breath diffusing capacity (\%Dco) was measured with a single breath diffusion system. The predicted normal values for VC and MVV were those of Baldwin et al\(^8\) and values for FRC, TLC, \( \text{FEV}_1 \), and \%Dco were those of Grimby et al\(^9\), Berglund et al\(^9\), and Burrows et al\(^9\), respectively.

Exercise testing was performed on a treadmill under continuous monitoring of ECG and blood pressure. The general guidelines for exercise testing\(^10\) were followed. Informed consent was obtained from all patients. The patients exercised on a treadmill following a continuous multistage schedule with a three-minute duration of each stage. Work increments were individually adjusted in order to have four to seven stages from rest to maximum work load. Generally, initial work load was started at the speed of 0.75 mile per hour (MPH) and zero grade incline followed by increments of 0.25 MPH speed and 2 to 4 percent grade at each stage. Expired gas was collected with a Douglas bag connected to the patient through a one-way J-valve (dead space 85 ml), and analyzed for \( \text{O}_2 \) and \( \text{CO}_2 \) by a gas analyzer. It was calibrated preexercise and postexercise using known gases that had been verified on a micro-Scholander. Expired gas volume was
Table 1—Anthropometric, Pulmonary Function, and Gas Exchange Data

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>46</td>
<td>28</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>59.3±8.2</td>
<td>60.5±7.2</td>
<td>57.5±9.5</td>
<td>ns</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>53.8±8.9</td>
<td>51.1±6.6</td>
<td>57.9±10.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Obesity index</td>
<td>97.3±13.2</td>
<td>92.8±11.6</td>
<td>104.5±12.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>14.4±0.9</td>
<td>14.4±0.9</td>
<td>14.5±1.0</td>
<td>ns</td>
</tr>
<tr>
<td>VC, %pred</td>
<td>81±16</td>
<td>86±14</td>
<td>73±15</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.09±0.49</td>
<td>0.98±0.37</td>
<td>1.27±0.56</td>
<td>0.05</td>
</tr>
<tr>
<td>FEV₁, %pred</td>
<td>47±18</td>
<td>43±14</td>
<td>54±23</td>
<td>0.1</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>44±15</td>
<td>37±9</td>
<td>54±16</td>
<td>0.01</td>
</tr>
<tr>
<td>FRC, %pred</td>
<td>108±21</td>
<td>118±17</td>
<td>93±19</td>
<td>0.001</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>51±7</td>
<td>53±6</td>
<td>43±8</td>
<td>0.01</td>
</tr>
<tr>
<td>TLC, %pred</td>
<td>105±16</td>
<td>112±14</td>
<td>94±13</td>
<td>0.001</td>
</tr>
<tr>
<td>DCO, ml/min/mm Hg</td>
<td>12.6±5.5</td>
<td>9.7±3.1</td>
<td>17.2±5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>DCO, %pred</td>
<td>73.6±26.7</td>
<td>59.1±18.8</td>
<td>96.0±21.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Vd/Vt, %</td>
<td>43.8±8.2</td>
<td>43.7±8.4</td>
<td>44.0±8.1</td>
<td>ns</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>78.6±8.5</td>
<td>80.2±6.5</td>
<td>76.2±10.6</td>
<td>ns</td>
</tr>
<tr>
<td>At rest</td>
<td>63.1±11.9</td>
<td>59.1±7.9</td>
<td>69.4±14.4</td>
<td>0.01</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>37.7±3.1</td>
<td>37.8±3.4</td>
<td>37.4±2.3</td>
<td>ns</td>
</tr>
<tr>
<td>At rest</td>
<td>43.6±6.1</td>
<td>44.9±6.7</td>
<td>41.8±4.3</td>
<td>ns</td>
</tr>
<tr>
<td>ΔPaO₂/ΔVO₂, mm Hg/L/min</td>
<td>−23.0±16.6</td>
<td>−32.4±12.7</td>
<td>−8.7±10.0</td>
<td>0.001</td>
</tr>
<tr>
<td>VO₂max, ml/min</td>
<td>1056±340</td>
<td>946±249</td>
<td>1227±396</td>
<td>0.01</td>
</tr>
</tbody>
</table>

PaO₂ measured with a dry gas meter. Inspiratory flow was recorded by a pneumotachometer in the inspiratory circuit, and respiratory rate was measured. From these data, minute ventilation, tidal volume, alveolar ventilation, oxygen uptake (Vo₂), carbon dioxide production (VCO₂), and Vd/Vt ratio were calculated using standard equations. 4

Arterial blood samples were drawn through a polyethylene catheter inserted into the brachial artery under local anesthesia. They were drawn into heparinized glass syringes during the collection of expired gas at rest in a standing position and during the last one minute of each exercise stage. Arterial blood gas tension values were measured with a blood gas analyzer.

For the quantitative analysis, PaO₂ was plotted against VO₂ from rest to maximum stage achieved, as shown in Figure 1. A regression equation was computed in all cases by the methods of least squares and a slope (ΔPaO₂/ΔVO₂) was obtained in each case. 5 From the linear regression, an estimation of PaO₂ at a VO₂ of 1.0 L/min was made (Fig 1). We compared the estimated PaO₂ thus obtained with the predicted PaO₂ which was calculated from our prediction equation described in the results.

All data are presented as means±SD. The two-tailed Student's t-test was used to compare mean values. Possible correlations between the slope and resting pulmonary function measurements were evaluated using single and multivariate linear regression analysis.

**RESULTS**

Mean values ±1 SD of the arterial blood gas levels at rest and during maximum exercise are presented in Table 1. The PaO₂ decreased by 15 mm Hg as a whole. The decreases were more pronounced in group A than

![Figure 1. Method of calculation of a slope (ΔPaO₂/ΔVO₂) and estimation of PaO₂ at a VO₂ of 1.0 L/min. For details see text.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21556/ on 04/28/2017)
in group B. The PaCO₂ significantly increased with maximum exercise suggesting the development of alveolar hypoventilation.

In most cases, the PaO₂ changed linearly in relation to ˙VO₂; 34 out of 46 patients showed statistically significant linear regression. In the other 12 patients who had small slope values, the regressions were not statistically significant simply because PaO₂ changes were small with increasing ˙VO₂. We included all data for the analysis.

The values of the slope (ΔPaO₂/Δ˙VO₂) ranged from +3.7 to −66 mm Hg/L·˙VO₂/min with a mean value of −23 mm Hg/L·˙VO₂/min (Fig 2). When group A and B were compared, the former had much larger negative values than the latter indicating the PaO₂ fell more steeply with exercise in group A patients.

Correlation between the slope and resting pulmonary function tests was computed to examine the feasibility of predicting PaO₂ change during exercise. The highest negative correlation was observed between the slope and %Dco (r = −0.851) as shown in Figure 3. The correlation between the slope and Dco itself was slightly lower (r = −0.783). Also, there were significant negative correlations between the slope and FEV₁/FVC (r = −0.545), %FEV₁ (r = −0.349) and %MVV (r = −0.355), but the correlation coefficients were much smaller. No correlation was found between the slope and %VC, RV/TLC, resting PaO₂, and VD/VT ratio.

By single regression analysis, the following equation was derived.

\[ \Delta \text{PaO}_2/\Delta \dot{\text{VO}}_2 \ (\text{Slope}) = -59.3 + 0.501 \times \% \text{Dco} \] Eq (1)

SEE (standard error of estimated value) = 8.35

\[ r^2 \ (\text{fraction of variance explained by regression}) = 0.72 \]

p<0.001

Expecting a further increase of the \( r^2 \) value, multivariate regression analysis combining %Dco with FEV₁/FVC, %FEV₁, and %MVV was performed. However, it yielded a minimal increase of \( r^2 \) values. Therefore, prediction of slope of the PaO₂ regression was possible from the measured %Dco alone using equation (1).

Knowing the slope and PaO₂ at rest, it is possible to predict PaO₂ at a given ˙VO₂ using the equation:

\[
\text{predicted PaO}_2 = \text{PaO}_2 \text{rest} + \text{SL} (\dot{\text{VO}}_2 \text{exc} - 0.25) \text{Eq (2)}
\]

where \( \text{SL} = \) predicted slope from measured %Dco

\( \dot{\text{VO}}_2 \text{exc} = \) oxygen uptake at a given workload and resting \( \dot{\text{VO}}_2 \) was assumed 0.25 L/min.
Before applying this predicting equation prospectively, we examined the relationship between the predicted PaO₂ at an \( \dot{V}_O_2 \) of 1.0 L/min and the estimated PaO₂ in original patients because two variables, PaO₂ at rest and assumed resting \( \dot{V}_O_2 \) were introduced in equation (2). There was a very high correlation between the two with an \( r \) value 0.898.

In order to verify our prediction, a prospective study was carried out with the latest series of COPD patients. Anthropometric and pulmonary function results of these patients are listed in Table 2. Twelve patients exercised on a treadmill following an identical protocol used in the retrospective study. The estimated PaO₂ at \( \dot{V}_O_2 = 1.0 \) L/min was derived in each case and compared with predicted PaO₂ calculated from resting PaO₂ and %Dco using equation (2) (Fig. 4). Eight out of the 12 cases were distributed in the shaded area. All seven patients with a predicted PaO₂ above 60 mm Hg had an estimated PaO₂ above 55 mm Hg, supporting the high specificity in excluding oxygen indicator, and all three patients with the estimated PaO₂ below 55 mm Hg showed the predicted PaO₂ below 60 mm Hg.

**Discussion**

We observed in patients with COPD that, when PaO₂ fell with exercise, the decrease was fairly linear in relation to oxygen uptake. The PaO₂ fell chiefly because of a widening of alveolar-arterial \( O_2 \) gradient, but a rise in PaCO₂ was partially responsible. This observation was consistent with many previous studies.1,3,4 We believe that the slope of the PaO₂ regression is clinically very important. It is obvious that, unless a change of PaO₂ during exercise is defined in relation to workload, an absolute change (\( \Delta \)PaO₂) itself has limited clinical as well as physiologic meaning. The slope was much steeper in group A patients (emphysematous) than group B patients (bronchitic). This agrees with previous observations that patients with emphysema tend to lower PaO₂ with exercise, whereas bronchitic patients do not.1 While there may exist several mechanisms that cause a linear fall of PaO₂ with increasing workload,16,17 we did not attempt to define these.

Values of the slope were most closely related with Dco among other parameters of resting pulmonary function tests. There are several studies describing an association of single breath diffusing capacity with arterial desaturation during exercise.6,18,19 Recently, Owens et al,6 using ear-oximeter, reported the single breath diffusion capacity was useful in terms of specificity and sensitivity in excluding arterial desaturation during exercise. But they found no linear correlation between \( O_2 \) desaturation (\( \Delta \text{SaO}_2/\Delta \dot{V}_O_2 \)) and the diffusing capacity; therefore, qualitative prediction was not possible from their study. This may be due to the difference in arterial oxygen saturation which Owens et al measured and the oxygen tension in the present investigation. A significant change in PaO₂ on a high and flat portion of the oxyhemoglobin dissociation curve would cause only minimal change in oxygen saturation, resulting in a significantly large \( \Delta \text{PaO}_2/\Delta \dot{V}_O_2 \) value with small \( \Delta \text{SaO}_2/\Delta \dot{V}_O_2 \). This may explain at least partly why they had a wide distribution of %Dco in a narrow range of \( \Delta \text{SaO}_2/\Delta \dot{V}_O_2 \) around zero value yielding a nonlinear relationship. We found a high linear correlation (\( r = 0.851 \)) between the slope and %Dco (Fig. 3). Evaluation of the slope using multivariate regression analysis with %Dco and FEV/FVC, %FEV\(_1\), or %MVV revealed no significant increase of \( r^2 \) values compared to that of single variate analysis with %Dco alone (\( r^2 = 0.72 \)). This means more than 70

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**Table 2—Anthropometric and Pulmonary Function Data of 12 Patients with COPD in Prospective Study**

<table>
<thead>
<tr>
<th>No.</th>
<th>12 (emphysematous 7, bronchitic 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>59.5 ± 9.7</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>55.5 ± 9.1</td>
</tr>
<tr>
<td>Obesity index</td>
<td>100.2 ± 15.4</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>13.8 ± 1.1</td>
</tr>
<tr>
<td>VC, %pred</td>
<td>86.5 ± 19.3</td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>1.39 ± 0.44</td>
</tr>
<tr>
<td>FEV(_1)/FVC, %</td>
<td>50.8 ± 16.6</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>45.1 ± 5.9</td>
</tr>
<tr>
<td>Dco, ml/min/mm Hg</td>
<td>13.2 ± 5.5</td>
</tr>
<tr>
<td>Dco, %pred</td>
<td>78.1 ± 32.8</td>
</tr>
<tr>
<td>PaO₂, rest mm Hg</td>
<td>83.1 ± 8.5</td>
</tr>
<tr>
<td>PaCO₂, rest mm Hg</td>
<td>36.9 ± 3.8</td>
</tr>
<tr>
<td>( \dot{V}_O_2 )max, L/min</td>
<td>1.06 ± 0.34</td>
</tr>
</tbody>
</table>

*Data are means ± 1SD.*

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1. \( C^2 \)
2. \( D^2 \)
3. \( E^2 \)
4. \( F^2 \)
5. \( G^2 \)
6. \( H^2 \)
7. \( I^2 \)
8. \( J^2 \)
9. \( K^2 \)
10. \( L^2 \)
11. \( M^2 \)
12. \( N^2 \)
13. \( O^2 \)
14. \( P^2 \)
15. \( Q^2 \)
16. \( R^2 \)
17. \( S^2 \)
18. \( T^2 \)
19. \( U^2 \)
20. \( V^2 \)
21. \( W^2 \)
22. \( X^2 \)
23. \( Y^2 \)
24. \( Z^2 \)
percent of the variation in the slope could be explained by the single resting parameter, \(\%D\text{CO}\). Therefore, the slope of the PaO\(_2\) regression with exercise was reliably predictable from the measured DCO. This, in turn, enabled us to predict PaO\(_2\) at a given \(\dot{V}O_2\) using equation (2). It should be noted here that prediction of the arterial desaturation during exercise is dependent not only on the slope (\(\Delta\text{PaO}_2/\Delta\dot{V}O_2\)), but also resting PaO\(_2\) and workload as well. Although resting oxygen uptake was assumed to be 0.25 L/min for simplicity, there was a high correlation between the predicted PaO\(_2\) and the estimated PaO\(_2\) at \(\dot{V}O_2 = 1.0\) L/min suggesting the clinical usefulness of the equation. The prospective study using unselected patients with COPD confirmed that the equation we proposed is valid in predicting PaO\(_2\) during exercise (Fig 4).

In using the equation, there may be concern about which normal predicted values for single breath diffusing capacity would be preferable to obtain percent predicted DCO. As there are wide variations in predicted values being attributed to many factors, a regression formula for DCO may not to be a specific one.\(^{20}\) We used Burrows’ regression formula\(^{20}\) because it fit best with values of normal subjects in our laboratory.

It must be considered that our prediction equation may be specific to the present exercise protocol because response of PaO\(_2\) to exercise can be influenced by the form of exercise and duration of each increment.\(^{31,32}\) We know from recent experiences using breath-by-breath monitoring of gas exchange indices that the patients were in semisteady state condition at the end of each work load. Thus, the PaO\(_2\) measured during exercise is considered to be that in steady-state of corresponding \(\dot{V}O_2\). In a patient with COPD, a transient fall in PaO\(_2\) at the start of exercise is reported to be small compared to normal subjects because of a slower rate of increase in tissue \(\dot{V}O_2\).\(^{22}\) In addition, one of the most widely used methods for exercise training in COPD is continuous walking,\(^{23,24}\) in which semisteady-state condition is expected. For these reasons, our prediction will be practical and useful as a guide for exercise programs in patients with COPD.

AKNOWLEDGMENT: The writers wish to thank Professor Kenneth M. Moser of University of California, San Diego Medical Center for his critical review of the manuscript.

REFERENCES