Hypoxemia During Altitude Exposure*
A Meta-Analysis of Chronic Obstructive Pulmonary Disease

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A previous study identified spirometric testing as a useful adjunct for estimating \( \text{PaO}_2 \) during altitude exposure in patients with chronic obstructive pulmonary disease (COPD). We sought to examine the validity of this finding by quantitative analysis of recent published reports. We analyzed acute hypoxemic exposures from five prior studies involving 71 patients. Across all studies, the change in arterial oxygen tension per unit change in inspired oxygen partial pressure (linear slope, d\( \text{PaO}_2 \)/d\( \text{P}_{\text{O}_2} \)) correlated with the preexposure forced expiratory volume in 1 s (FEV1, \( p<0.01 \)). The correlation with FEV1 held for values weighted or unweighted by sample size, with rotating deletion of each study from analysis one at a time, and with final hypobaric exposures (Table 1 of 6). We sought to develop quantitative indices of response to hypoxic exposure that could serve as variables common to all studies and thereby allow comparisons between studies.

The ambient conditions inside commercial aircraft expose passengers to hypobaric hypoxia often approaching the altitude equivalent of 8,000 feet (2,438 m) above sea level. Clinical guidelines recommend that supplemental oxygen should be prescribed if predicted arterial blood oxygen tension would fall below 50 mm Hg during flight. Several methods exist for estimating air travel hypoxemia. For patients who live at elevations above sea level, however, no existing mathematical formula for estimating \( \text{PaO}_2 \) during air travel adjusts for a starting altitude significantly above sea level.

A few earlier studies addressed the clinical problem of hypoxic exposure in patients with chronic obstructive pulmonary disease (COPD). Patients in these studies had some differences in the severity of airflow obstruction and gas exchange disturbance (Table 1). Also, hypoxic exposures in earlier studies include the use of hypoxic gas inhalation at constant altitude to simulate altitude conditions and differing initial and final hypobaric exposures (Table 1 of 6). We sought to develop quantitative indices of response to hypoxic exposure that could serve as variables common to all studies and thereby allow comparisons between studies.

We also sought evidence as to the validity of the forced expiratory volume in 1 second (FEV1) as a predictor of change in arterial oxygen tension with hypoxic exposure in patients with COPD. An earlier study reported that FEV1 improved description of the change in \( \text{PaO}_2 \) with altitude exposure in patients with COPD compared with ground level \( \text{PaO}_2 \) alone.

We undertook this meta-analysis for additional reasons, among them the invasiveness of arterial catheter studies, the relatively small size of each separate published study, and the low likelihood that a prospective study from different starting and ending altitudes would be done in the near future.

**METHODS**

We evaluated mean hypoxemic responses from five published studies involving 71 patients with COPD. We searched for studies of patients with COPD published since 1966 that involved acute hypoxic exposure and also reported mean values for arterial blood oxygen tensions before and after exposure, barometric pressure \( (P_b) \) or altitude conditions, fraction of inspired oxygen \( (F_{\text{I}O_2}) \) if other than ambient air, and results of spirometry, specifically FEV1.

We developed two measures of hypoxic exposure common to all studies in order to facilitate comparisons. The first, linear slope, consisted of the change in arterial oxygen tension per unit change in inspired oxygen tension (equation 1):

\[
\text{linear slope} = \frac{(\text{PaO}_2\text{alt} - \text{PaO}_2\text{g})/(	ext{P}_{\text{O}_2}\text{alt} - \text{P}_{\text{O}_2}\text{g})}{\text{PaO}_2(\text{alt}) - \text{PaO}_2(\text{g})}
\]

The postscripts alt and g refer to "altitude" and "ground" values, respectively. A second measure, the semilog slope, differed from linear slope only in that the numerator, but not the denominator, consisted of the difference of natural logarithms (equation 2):

\[
\text{semilog slope} = \text{ln}(\text{PaO}_2\text{alt}/\text{PaO}_2\text{g}) = k \cdot (\text{P}_{\text{O}_2}\text{alt} - \text{P}_{\text{O}_2}\text{g})
\]
Table 1 — Values for Selected Variables From Prior Studies of Patients With COPD Exposed to Hypoxic Conditions*

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample (N)</th>
<th>Barometric Pressure, mm Hg</th>
<th>Elevation, m</th>
<th>PO₂, mm Hg</th>
<th>FEV₁, L</th>
<th>Linear Slope</th>
<th>Semilog Slope</th>
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<tr>
<td>Graham and Houston⁴</td>
<td>8</td>
<td>756 602</td>
<td>50</td>
<td>1920</td>
<td>148</td>
<td>116</td>
<td>1.270</td>
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<tr>
<td>Matthys et al⁵</td>
<td>10</td>
<td>720 560</td>
<td>450</td>
<td>2500</td>
<td>141</td>
<td>107</td>
<td>1.400</td>
</tr>
<tr>
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<td>755 623</td>
<td>SL</td>
<td>1650</td>
<td>148</td>
<td>120</td>
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<td>22</td>
<td>754 754*</td>
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<td>2438</td>
<td>148</td>
<td>107</td>
<td>1.100</td>
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<td>Dillard et al⁶</td>
<td>18</td>
<td>758 565</td>
<td>SL</td>
<td>2438</td>
<td>148</td>
<td>108</td>
<td>0.975</td>
</tr>
</tbody>
</table>

*PO₂ = inspired oxygen partial pressure; G = ground; Alt = altitude; FEV₁ = forced expiratory volume in 1 second; SL = sea level.

†Normobaric hypoxia, FIO₂ = 0.151.

The semilog slope is given by:

\[ \text{semilog slope} = \frac{\ln(\text{PaO}_2\text{alt}) - \ln(\text{PaO}_2\text{ref})}{(\text{P}_0 - 47) \times \text{FIO}_2} \]

We chose these particular indices because they involve familiar terms and easy calculations; however, other mathematic approaches may be equally acceptable.

We included the mean values (Table 1) from published articles for analysis.** We did not include subsets within a study with incomplete or unbalanced observations. We included one pair of exposures per study (Table 1). We converted altitude values to P₀ using a table.³ We calculated inspired oxygen tension (P₁O₂) as (P₀ - 47) times FIO₂. This represents inspired air saturated with water vapor.

One study used hypoxic gas inhalation (FIO₂ = 0.151) to simulate altitude exposure at constant P₀ (normobaric hypoxia). The data in Table 1 for all other studies represent hypobaric exposures. We obtained numeric values from one study by measuring scaled graphs with calipers. For one study we calculated mean FEV₁ using the reported FEV₁ percent of predicted and the specified prediction standards.³³

Computations used SPSS/PC +.³ We present data as mean ± SD unless otherwise noted. When used, we weighted values by the number of patients in a given study (Table 1). Correlations refer to least squares linear fit. We report two-tailed p values less than 0.05 as significant.

RESULTS

Table 1 presents mean values for selected data from the five studies involving 71 patients. Age varied from 53 to 68 years in the studies. The weighted mean age equaled 64 ± 5 years (n = 61). Mean values for FEV₁ in the separate studies ranged from 0.975 to 1.400 L. Each study provided sufficient data for computation of linear and semilog slopes (Table 1, Fig 1).

Linear slope (Table 1), the change in PaO₂ per unit change in P₁O₂ as defined in equation 1, correlated with FEV₁ in a negative direction (p = 0.0048) (Fig 2). Thus, the largest rate of decline in PaO₂ per unit change in P₁O₂ occurred in the samples with lowest values for FEV₁. Table 1 shows that the largest linear slope, or rate of decline in PaO₂, occurred in the study with the lowest mean FEV₁.

Removal of each study from analysis one at a time in rotation did not remove the correlation (p ≤ 0.0337) for any of the five combinations of five studies considered four at a time (Table 2). The above findings held for values unweighted or weighted by study sample size. Values for semilog slope (equation 2) correlated with FEV₁ (p = 0.0021) also in a negative direction and more strongly than linear slope (Table 2).

Predicted values for PaO₂ at altitude derived from the regression of semilog slope on FEV₁ agreed with observed mean values within ±1.0 mm Hg. We calculated the predicted values in Table 1 from the following equation (3):

\[ \text{PaO}_2\text{alt} = [\text{PaO}_2\text{ref}] \times e^{(-k_4 \times x)} \]

Table 2 — Correlations Between FEV₁ and Linear Slope for Weighted and Unweighted Samples

<table>
<thead>
<tr>
<th>Deletion*</th>
<th>Weight,</th>
<th>p</th>
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<td>r†</td>
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<tr>
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<td>Schwartz et al⁶</td>
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</tr>
<tr>
<td>Gong et al⁶</td>
<td>4</td>
<td>0.991</td>
</tr>
<tr>
<td>Dillard et al⁶</td>
<td>4</td>
<td>0.952</td>
</tr>
</tbody>
</table>

*Specified study deleted from analysis.
†Coefficient of determination using mean values.
where \( x = P_{1O_2 \text{g}} - P_{1O_2 \text{alt}} \); \( e = 2.71828 \), the base of the exponential function; and the asterisk indicates multiplication. An equivalent expression consists of (equation 4):

\[
\ln(P_{O_2 \text{alt}}/P_{O_2 \text{g}}) = k_s \cdot (P_{O_2 \text{alt}} - P_{O_2 \text{g}}).
\]

The coefficient \( k_s \) could take several values. One value, \( k_s = 0.02002 - 0.00976 \times \text{FEV}_1 (L) (n = 71) \), was derived from linear regression of semilog slope on \( \text{FEV}_1 \).

Equations 3 and 4 present \( \text{PaO}_2 \text{alt} \) as a function of the change in inspired oxygen partial pressure from an initial ground \( \text{PaO}_2 \) value. \( \text{FEV}_1 \) modulates the relationship in this model. Available data did not permit analysis of other possible determinants of the coefficient \( k_s \) although other predictors, such as age or other variables, may be equally plausible or preferable.

We developed equation 3 from the weighted mean data from 71 patients. We then examined the results of predictions from individual data for 18 patients with \( \text{FEV}_1 \) ranging from 0.52 to 1.60 L. This subset, though partially nested, did not determine 75 percent of the weighted sample determining equation 3. The analysis found 95 percent confidence intervals for residuals (observed minus predicted values for \( \text{PaO}_2 \text{alt} \)) of \(-2.90 \) to 1.26 mm Hg for the 18 patients. Predicted values from equation 3 correlated with observed values \((r = 0.830, p < 0.0001, n = 18)\) with a slope and intercept that did not differ from an identity relationship (slope 0.998, intercept 0.905).

Predictions of \( \text{PaO}_2 \text{alt} \) from the regression of linear slope (equation 1) on \( \text{FEV}_1 \), correlated with observed values in the individual sample but not in an identity relationship (slope 1.388, intercept \(-17.470\)). This finding favors the semilog over the linear slope method. Figure 3 shows the superiority of the semilog slope index over the linear slope index to predict mean values of \( \text{PaO}_2 \) for each study.

We also calculated an alternate value for the coefficient \( k_s \), \( k_s^* \), which incorporates \( \text{FEV}_1 \) percent of predicted\(^10\) into equation 3. For this application \( k_s^* = 0.01731 - 0.00019 \times \text{FEV}_1 (L) \) percent predicted where \( \text{FEV}_1 \) does not exceed 60 percent predicted. Use of \( k_s^* \) in equation 3 gave residuals comparable to \( k_s \) and gave the same mean predicted value for Gong et al\(^2\) (Table, 47.11).

**Discussion**

We evaluated studies involving a specific disease entity with a finite range of inspired oxygen partial pressure. We do not expect the slope indices to correlate with \( \text{FEV}_1 \) in normal subjects. The indices of hypoxia which we developed, however, may be applicable to other patient care settings involving changes in inspired oxygen partial pressure.

The present study provides further evidence of the utility of \( \text{FEV}_1 \) as a predictor of \( \text{PaO}_2 \) during altitude exposure in COPD patients.\(^3\) In COPD and other lung diseases, \( \text{FEV}_1 \) often may not correlate strongly with \( \text{PaO}_2 \); however, use of a patient’s initial \( \text{PaO}_2 \) as a predictor of final \( \text{PaO}_2 \) adjusts for some of the between and within subject variability. This, we believe, permits \( \text{FEV}_1 \) to be a second-order predictor of \( \text{PaO}_2 \) at altitude.\(^3\) Also, relatively large altitude-induced changes in \( \text{PaO}_2 \) in stable patients may allow correlation with \( \text{FEV}_1 \), not ordinarily expected from cross-sectional or day-to-day associations between \( \text{PaO}_2 \) and \( \text{FEV}_1 \) at constant altitude.

We presume, in this context, that \( \text{FEV}_1 \) may be a surrogate for physiologic variables that influence impedance to ventilation. Conceivably, \( \text{FEV}_1 \) may be a surrogate for other variables such as age, ventilatory drive, ventilation-perfusion matching, or other variables. The number of potential determinants for \( \text{PaO}_2 \) at altitude appears large. The full range of variables has likely not been fully explored in any studies to date.

We found linear and semilog slopes permitted comparison of the different studies. Greater slope
correlated with lower FEV₁ in a negative direction. These findings support an earlier report⁸ that measurement of FEV₁ improved prediction of altitude hypoxemia in patients with COPD. The present study provides a unified description of the available data pertaining to this clinical problem.

Subject to verification, equation 3 of the present study may have utility at starting elevations above sea level. An equation from a previous report⁸ should be used from a starting point at sea level to predict PaO₂ at 8,000 feet.

The results show that, in general, subjects with lower values for FEV₁ have lower values for PaO₂ at altitude when ground PaO₂, and change in P₁O₂ are the same for all subjects. This finding appears to justify measuring FEV₁ in patients who propose to travel by air. We recommend measurement of FEV₁ as part of routine preflight assessment for patients with COPD.

The present study showed closer average agreement between hypoxic gas inhalation⁷ and hypobaric exposure⁸ than previously reported.⁸ Hypoxic gas inhalation may be a useful test to consider in many clinical situations. We favor performance of additional studies to evaluate the agreement between hypoxia inhalation testing (HIT) and actual hypobaric exposure.

The use of regression equations for predicting PaO₂ during air travel remains appropriate both to screen patients for hypoxic gas inhalation and as a definitive step in locations without hypoxic gas testing. Regression equations incorporating FEV₁ appear preferable to equations or nomograms that do not include this variable.

All of the published studies had a preponderance of male subjects. Due to nonuniform reporting,⁴ the present study did not investigate FEV₁ as percent predicted as extensively as FEV₁ in liters. Use of FEV₁ percent of predicted has some potential advantages over FEV₁ in liters.⁸

The barometric pressure at a starting elevation determines P₁O₂g in equation 3. Equation 3 could be adapted to depend on P₈ instead of P₁O₂ for situations not involving hypoxic gas inhalation.

Though nonlinear, equation 3 poses no computation hardship for personal computers or scientific calculators. Also, for the purposes of equation 3, the P₁O₂alt at 8,000 feet (P₈ = 565) equals (565 - 47) * 0.209 or 108 mm Hg, a useful value for P₁O₂alt for many flights.

The findings of this report apply to patients with COPD without other defects in oxygen transport or critical organ perfusion. These results should not be assumed applicable to normal subjects, hypercapnic patients, or patients with COPD and additional defects.

In summary, we developed methods for comparison of nonuniform hypoxic exposures. We found evidence confirming FEV₁ as a correlate of hypoxemia during altitude exposure and developed a prediction model capable, subject to verification, of incorporating variations in hypoxic exposures for patients with COPD.

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