Does the Hypoxic Ventilatory Response Predict the Oxygen-induced Falls in Ventilation in COPD?*

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The purpose of this study was to determine whether supplemental oxygen-induced decreases in ventilation (Ve) and mouth occlusion pressure (P0.1) in patients with COPD are related to the ventilatory or P0.1 responses to hypoxia (ΔVe/ΔSaO2, ΔP0.1/ΔSaO2). We measured these responses in 14 patients with a (mean ± SD) FEV1 of 0.95 ± 0.41 L. The Ve and P0.1 were also measured while the patients sequentially breathed either room air or supplemental oxygen (1-2 L/min) for 10 min in a randomized single blind fashion. The mean (±SEM) SaO2 increased from 90.8 ± 0.99 percent to 95.2 ± 0.46 percent and the Ve decreased during oxygen breathing from 12.3 ± 0.46 to 11.6 ± 0.47 L/min (p<0.03). However, the individual changes in Ve were not significantly related to the corresponding changes in SaO2 (CHG SaO2), (ΔVe/ΔSaO2), or (ΔVe/SaO2) (CHG SaO2). Similarly, the P0.1 decreased from 2.50 ± 0.27 to 2.26 ± 0.20 cm H2O (p<0.05), but the individual changes in P0.1 were not significantly related to (CHG SaO2), (ΔP0.1/ΔSaO2), or (ΔP0.1/ΔSaO2) (CHG SaO2).

CHG = changes; FRC = functional residual capacity; PETCO2 = end-tidal Pco2; P0.1 = mouth occlusion pressure; PREDCHG = "predicted" changes

Many patients with COPD, even if only mildly hypoxicemic, claim to be less dyspneic at rest when they are receiving supplemental oxygen. Although a placebo effect may be important in some of these patients, previous studies have demonstrated that exercise tolerance and breathlessness during exercise do improve in these patients while they breathe supplemental oxygen.1,2 Swinburn and coworkers3 have also recently demonstrated that hypoxicemic and breathless patients with COPD had a reduction in ventilation and dyspnea at rest during oxygen breathing. They hypothesized that the fall in ventilation was due to a reduction in the hypoxic drive to breathe. However, some patients with COPD complain of dyspnea at rest despite having resting arterial oxygen saturations (SaO2) well above 90 percent. In fact, many patients who fit the category of "pink puffer" complain the most vehemently about being short of breath. Criner and Celli4 showed that oxygen breathing in patients less hypoxicemic than those evaluated by Swinburn and coworkers3 does reduce the minute ventilation (Ve). If the fall in ventilation in these patients was secondary to a reduction in ventilatory drive as suggested above, we hypothesized that those individuals with the greatest hypoxic drive would have the largest reductions in their Ve and mouth occlusion pressures (P0.1).

This study had two objectives: (1) to determine if the Ve and the P0.1, an index of respiratory drive,5 were reduced when mildly hypoxicemic patients received supplemental oxygen; and (2) to determine if the reductions in ventilation and P0.1 were related to the hypoxic drive.

METHODS

Fourteen patients with moderate to severe airflow limitation and meeting the American Thoracic Society criteria for COPD were studied. These patients had a mean (±SD) age of 63.9 ± 7.5 years. The project was approved by the institutional review board of our hospital. Patients gave written informed consent before participating in the project.

Patients were studied while breathing on a mouthpiece with a nose clip in place. The mouthpiece was connected to a Hans-Rudolph mouth occlusion pressure apparatus that consisted of an occlusion balloon and one-way inspiratory valve on the inlet side and a one-way expiratory valve on the outlet side. The balloon could be occluded during exhalation. Reservoir tubing was connected to the inlet side and either medical grade air or oxygen at a flow of 1 or 2 L/min was infused. The flow of oxygen was selected to ensure an arterial saturation greater than 94 percent. A turbine (Alpha Technology) was connected to the expiratory side and this allowed measurement of Ve. The patients sequentially breathed either room air or oxygen in random order. The two measurement periods were 10 min in duration and were separated by 30 min. The patients breathed on the circuit for 5 min before measurements began. They were blind to the type of gas infused (single blind). A pressure tap at the mouthpiece was connected to a pressure transducer (Validyne). The mouth occlusion pressure developed in the first 100 ms of inspiration (P0.1) was measured and displayed digitally with a custom-designed device that has for its basis two sample and hold chips. This device controlled a noiseless pneumatic valve that produced occlusion of the inspiratory airway during
expiration and released the occlusion after the first 0.2 s of inspiration. The SaO₂ was measured by an ear oximeter (Hewlett-Packard 47201 A). Every minute during the 10-min study periods, measurements of VE, PO₁, and SaO₂ were obtained and the results were averaged.

**Hypoxic Responses**

The ventilatory and PO₁ responses to hypoxemia were measured within 48 h of the above tests utilizing the technique of Reh buck and Campbell. The SaO₂ was monitored with an ear oximeter (Hewlett-Packard 47201 A). After the subject had been seated comfortably and the mouthpiece and nose clip were in place, rebreathing was started from the bag primed with the subject’s own expired air. During the rebreathing, the end-tidal PCO₂ (PETCO₂) was kept constant at the subject’s prerebreathing end-tidal PCO₂ level with a soda lime CO₂ absorber connected to a variable-speed pump. Tidal volume was measured with a rolling seal spirometer. The PETCO₂ was monitored at the mouth with a rapid CO₂ analyzer (Beckman LB2). Mouth pressure was recorded with a differential pressure transducer. Tidal volume, mouth pressure, PETCO₂, and SaO₂ were continuously recorded on a four-channel recorder (Hewlett Packard 7754B). Approximately every 15 s without the subject’s knowledge, the inspiratory side of the rebreathing circuit was occluded for less than 0.2 s with a noiseless and vibration-free pneumatic valve. The mouth pressure developed in the first 100 ms of inspiration was measured from mouth pressure tracings. The saturation was allowed to fall to 75 percent before the study was terminated. After completion of the tests, ventilation and PO₁ were plotted against SaO₂ and the slope of the responses (ΔVE/ΔSaO₂, ΔPO₁/ΔSaO₂) and the intercepts were obtained by least-squares regression.

Student’s paired t test was used to compare the data for the individual subjects. The changes (CHG) in ventilation and PO₁ when subjects breathed oxygen were defined as CHG Vₑ = Vₑ room air – Vₑ oxygen and CHG PO₁ = PO₁ room air – PO₁ oxygen. The change in SaO₂ was CHG SaO₂ = SaO₂ oxygen – SaO₂ room air. We computed “predicted” changes in Vₑ and PO₁ (PREDCHG Vₑ and PREDCHG PO₁) during oxygen breathing by multiplying the slope of the appropriate hypoxic responses (ΔVE/ΔSaO₂, ΔPO₁/ΔSaO₂) by the change in SaO₂ (CHG SaO₂). The relationships between the variables CHG Vₑ, CHG PO₁, CHG SaO₂, ΔVE/ΔSaO₂, ΔPO₁/ΔSaO₂, PREDCHG Vₑ, and PREDCHG PO₁ were evaluated with linear regression using the least squares technique. Average values are displayed as the mean ± SEM unless otherwise stated.

**RESULTS**

The subjects had moderate to severe COPD with a mean (±SD) FEV₁ of 0.95 ± 0.41 L and an FVC of 2.29 ± 0.59 L. The SaO₂ for the 10-min monitoring period (mean ± SEM) was 90.8 ± 0.99 percent (range, 84 to 98) during room air breathing and 95.2 ± 0.46 percent during oxygen breathing. Supplemental oxygen increased the SaO₂ by 4.45 ± 0.66 percent and reduced the ventilation from 12.3 ± 0.46 L/min to 11.6 ± 0.47 L/min (p < 0.03). The mean ventilation values for the individual subjects during the 10-min period breathing air or supplemental oxygen are shown in Figure 1. The mean CHG Vₑ was 0.68 ± 0.27 L/min. The PO₁s were also reduced by supplemental oxygen from 2.50 ± 0.27 cm H₂O to 2.26 ± 0.20 cm H₂O (p < 0.05). The mean CHG PO₁ was 0.24 ± 0.11 cm H₂O. In Figure 2, the mean values of the PO₁ for

**FIGURE 1.** The mean minute ventilation values during room air and supplemental oxygen breathing for the individual subjects are displayed. The open circles represent the group means. Minute ventilation was significantly decreased during oxygen breathing (p < 0.03).

**FIGURE 2.** Individual mean mouth occlusion pressure values (PO₁) during room air and supplemental oxygen breathing are displayed. The open circles represent the group means. The mouth occlusion pressure decreased during oxygen breathing (p < 0.05).
The ventilation vs SaO₂ slopes (ΔVE/ΔSaO₂) obtained from the measurement of the hypoxic ventilatory response varied between −0.22 and −2.44 L/min/percent SaO₂ with a mean of −0.74 ± 0.15 L/min/percent SaO₂. The intercepts varied from 30.35 to 265.1 L/min. The mean intercept was 84.2 ± 114.3 L/min. The mean of the correlation coefficients for ventilation versus SaO₂ for the individual subject during hypoxic ventilation testing was 0.85 ± 0.04. The P0.1 versus SaO₂ slopes (ΔP0.1/ΔSaO₂) varied between −0.13 and −1.85 cm H₂O/percent SaO₂ with a mean of −0.51 ± 0.12 cm H₂O/percent SaO₂. The intercepts varied from 14.1 to 179.7 cm H₂O. The mean intercept was 50.8 ± 11.6 cm H₂O. The mean of the correlation coefficients for the individual subjects relating P0.1 to SaO₂ in the hypoxic P0.1 response tests was −0.85 ± 0.03.

There was no significant relationship between the supplemental oxygen-induced changes in ventilation or P0.1 (CHG VE, CHG P0.1) for the individual subjects and the "predicted" changes in VE and P0.1, respectively (Table 2) that were computed using the slopes of the hypoxic responses and the changes in SaO₂ (FREDCHG VE = (ΔVE/ΔSaO₂) × [CHG SaO₂]; FREDCHG P0.1 = (ΔP0.1/ΔSaO₂) × [CHG SaO₂]). The values of measured and predicted changes in ventilation for the individual subjects are depicted in Figure 3. Moreover, when the changes in VE or P0.1 for each individual were related to the slopes or intercepts of the hypoxic ventilatory or mouth occlusion responses respectively, the correlation coefficients were small and not statistically significant (Table 2).

**DISCUSSION**

Our study demonstrates that oxygen administration reduces the VE in mildly hypoxemic patients with COPD. As our study was performed in a single-blind manner, these findings were not due to a placebo effect. Previous studies⁵,⁶ have also found a reduction in ventilation during oxygen breathing in patients with COPD. In our study, the reduction in ventilation during oxygen breathing was accompanied by a reduction in the P0.1 (an index of respiratory drive). A significant relationship between the reduction in ventilation and the reduction in P0.1 was also noted. However, the reduction in ventilation was not related either to the baseline oxygen saturation or to the slope of the hypoxic ventilatory response. Similarly, the reduction in P0.1 was not related to the baseline oxygen saturation or the slope of the hypoxic P0.1 response. When we computed a predicted change in ventilation or P0.1 based on the slopes of the respective hypoxic response curves and the change in oxygen saturation, we still found no relationship between these derived values and the actual changes in ventilation or P0.1.

Our failure to find a correlation between the hypoxic responses and the falls in ventilation or P0.1 could have been due to either deficiencies in our experimental design or to errors in the assumptions underlying our hypothesis that such a relationship might exist. With respect to our experimental design, one problem with our analysis is the small magnitude of the falls in ventilation and P0.1 with oxygen. These falls may be too small to be clinically significant. One could argue that what we measured was little more than random variation. However, the fact that the falls in ventilation

### Table 1 — Correlation of Changes in VE and P0.1 During Oxygen Breathing*

<table>
<thead>
<tr>
<th></th>
<th>R†</th>
<th>P</th>
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<tbody>
<tr>
<td>CHG VE vs SaO₂-room air</td>
<td>−0.36</td>
<td>0.19</td>
</tr>
<tr>
<td>CHG VE vs FEV₁</td>
<td>−0.23</td>
<td>0.43</td>
</tr>
<tr>
<td>CHG VE vs CHG SaO₂</td>
<td>0.27</td>
<td>0.34</td>
</tr>
<tr>
<td>CHG P0.1 vs SaO₂-room air</td>
<td>−0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>CHG P0.1 vs FEV₁</td>
<td>−0.59</td>
<td>0.03</td>
</tr>
<tr>
<td>CHG P0.1 vs CHG SaO₂</td>
<td>−0.16</td>
<td>0.59</td>
</tr>
</tbody>
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*Abbreviations expanded in text.
†R = correlation coefficient.

### Table 2 — Relationships Between Changes in Ventilation and P0.1 During Oxygen Breathing and Hypoxic Responses*

<table>
<thead>
<tr>
<th></th>
<th>R†</th>
<th>P</th>
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<tbody>
<tr>
<td>CHG VE vs PRED CHG VE</td>
<td>0.17</td>
<td>0.56</td>
</tr>
<tr>
<td>CHG P0.1 vs PRED CHG P0.1</td>
<td>0.44</td>
<td>0.10</td>
</tr>
<tr>
<td>CHG VE vs ΔVE/ΔSaO₂</td>
<td>0.36</td>
<td>0.20</td>
</tr>
<tr>
<td>CHG VE vs intercept</td>
<td>−0.37</td>
<td>0.18</td>
</tr>
<tr>
<td>CHG P0.1 vs ΔP0.1/ΔSaO₂</td>
<td>−0.40</td>
<td>0.15</td>
</tr>
<tr>
<td>CHG P0.1 vs intercept</td>
<td>0.41</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Abbreviations expanded in text. CHG VE = VE on room air—VE on oxygen; CHG SaO₂ = SaO₂ on oxygen—SaO₂ on room air; CHG P0.1 = P0.1 on room air—P0.1 on oxygen; PRED CHG VE = (ΔVE/ΔSaO₂) × [CHG SaO₂]; PRED CHG P0.1 = (ΔP0.1/ΔSaO₂) × [CHG SaO₂].
†R = correlation coefficient.

**Figure 3.** The mean changes in ventilation with supplemental oxygen breathing for the individual subjects versus the predicted changes in ventilation ([ΔVE/ΔSaO₂] × [CHG SaO₂]).
did correlate with the falls in P0.1 argues against this supposition. Another possibility for a lack of correlation between the hypoxic responses and the decreases in ventilation during oxygen breathing is the within-subject variability in such measurements. For example, Rebuck and Campbell found a day-to-day variance of 0.76 in the slopes of the VE versus SaO2 curve in five normal subjects. In our study, the slopes of 13 of 14 subjects covered a range of only -0.22 to -1.02 L/min/percent SaO2. Therefore, the intrinsic variability in measurement of the slopes may have decreased the chance of finding a relationship between the changes in ventilation and the hypoxic ventilatory response. In addition, one must consider the effects of Pco2 on ventilation and ventilatory drive. Our hypoxic ventilatory response studies were conducted under eucapnic conditions as is standard procedure. During oxygen administration, we did not control the Pco2. Oxygen administration could have increased the Pco2 to a variable degree and this may have altered the hypoxic ventilatory drive or ventilation.

In summary, the combination of small changes in ventilation and P0.1 with oxygen, variability in the hypoxic ventilatory and P0.1 responses, and failure to ensure that the same Pco2 was present in the hypoxic response testing and oxygen-breathing trials may have reduced our ability to find a relationship between changes in the ventilation and P0.1 with oxygen breathing and the hypoxic responses. Having said this, one still might expect that patients with relatively high hypoxic responses would still show a greater drop in ventilation with oxygen.

We measured the hypoxic ventilatory response with the clear understanding that this is NOT a good measure of ventilatory drive in patients with mechanical limitation. However, our hypothesis that the degree of fall in ventilation with oxygen therapy might depend on the slope of the hypoxic response was based on the fact that the increase in ventilation as the SaO2 falls during progressive hypoxia is roughly linear and proportional to the fall in SaO2 ([CHG VE] = [ΔVE/ΔSaO2]/[CHG SaO2]). However, in a given patient, the same linear relationship between falls in SaO2 below baseline and the concomitant increases in ventilation may not hold for increases in SaO2 above baseline and the concomitant decreases in ventilation. That is, the ventilation versus SaO2 relationship in a given patient may be linear or have a different slope when the SaO2 is rising rather than falling. If that were the case, one would not expect a correlation between the slopes of the hypoxic ventilatory response curves and the fall in ventilation.

Another problem with our hypothesis is that it does not consider the effects on ventilation due to changes in Pco2 induced by oxygen breathing. One can express ventilation as a function of SaO2 and Pco2. If so, it is possible to analyze changes in ventilation when both the saturation and the Pco2 change using partial derivatives. If \( f = f(x, y) \), then by elementary calculus, \( df = (\partial f/\partial x) \, dx + (\partial f/\partial y) \, dy \). The change in ventilation when both SaO2 and Pco2 change may be expressed as \( \Delta V = (\partial V/\partial SaO2) \, \Delta SaO2 + (\partial V/\partial Pco2) \, \Delta Pco2 \) where \( (\partial V/\partial SaO2) \) represents the slope of the hypoxic ventilatory response measured at the initial Pco2 and \( (\partial V/\partial Pco2) \) represents the slope of the hypercapnic ventilatory response measured at the initial SaO2. As \( (\partial V/\partial SaO2) \) is a negative number and \( (\partial V/\partial Pco2) \) is a positive number, the first and second terms have opposing influences on \( \Delta V \). Our hypothesis is equivalent to assuming that the magnitude of the first term is much greater than the second. We did not measure \( \Delta Pco2 \) but studies in similar stable COPD patients breathing comparable concentrations of oxygen have shown an increase in Pco2 of about 2 mm Hg. If one uses a mean value for \( (\partial V/\partial Pco2) \) of 0.8 L/min/mm Hg, this gives an estimate of the magnitude of the second term of 1.6 L. The mean value of the first term was 2.68 L/min. The difference in these terms is about 1 L/min, which is much closer to the measured value for the CHG VE of 0.68 L/min than the first term alone. Thus, ignoring the effects of changes in Pco2 may be the main reason we did not find a correlation between the change in ventilation and either \( (\Delta V/\Delta SaO2) \) or \( (\Delta V/\Delta SaO2) \). For the above reasons, we believe that the hypoxic ventilatory response measured under eucapnic conditions and falling SaO2 values may have little relevance to changes in ventilation during oxygen breathing when the Pco2 is not fixed.

Other investigators have tried to relate the hypoxic ventilatory or mouth occlusion responses in COPD patients to the sensation of dyspnea or exercise performance. Robinson and coworkers found that the hypoxic P0.1 response did not correlate with the 6-min walk distance or the degree of dyspnea. Light et al found that the hypoxic response could not predict those COPD patients who would improve their exercise tolerance when given supplemental oxygen. In the present study, we also were unable to show a relationship between the hypoxic responses and the degree of reduction in ventilation or ventilatory drive with supplemental oxygen.

We did find a relationship between the changes in P0.1 during oxygen breathing and the FEV1. This may be explained in part by the dependence of the room air P0.1 on the FEV1. Robinson et al found an inverse relationship between the resting P0.1 and the percent predicted FEV1. In our study, a similar relationship was present but did not reach statistical significance. In any case, mechanics rather than the response of the ventilatory drive to worsening hypoxia may be the most important factor determining the "baseline" P0.1
and the subsequent decrease in P0.1 with oxygen administration.

We did not measure changes in functional residual capacity (FRC) during oxygen breathing. Although changes in FRC could potentially alter the P0.1 by reducing the pressure generated for a given amount of neural input, studies in normal subjects have shown no consistent changes in P0.1 with changes in FRC.15 In the study of Criner and Celli,4 oxygen breathing did not alter the pleural pressure at end exhalation during tidal breathing. This implies that FRC did not change. Thus, it is unlikely that the reductions in P0.1 during oxygen breathing were due to changes in FRC.

In summary, our study found that although oxygen administration caused small but statistically significant reductions in the VE and P0.1 in a group of patients with COPD and mild hypoxemia, the changes in ventilation and P0.1 were not related solely to any measure obtained from the hypoxic ventilatory or P0.1 responses.

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Prediction of Oxygen-induced Falls in Ventilation (Berry et al)