EFFECT OF OXYGEN TENSION OF INSPIRED AIR ON THE
RESPIRATORY RESPONSE OF NORMAL SUBJECTS
TO CARBON DIOXIDE

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Opinions have differed widely concerning the influence of the alveolar
oxygen tension on the respiratory response to carbon dioxide. Vernon
(15) believed that high oxygen tensions decreased the respiratory response
to carbon dioxide. Lindhard (9) and Hasselbalch and Lindhard (7) held
that the respiratory center became more sensitive to carbon dioxide as the
oxygen tension decreased. Campbell, Douglas, Haldane and Hobson (3)
maintained that the alveolar oxygen tension could be varied within wide
limits without sensibly affecting the respiratory response to carbon dioxide.
The work of Eastman (5) and Selladurai and Wright (12) showed that the
respiratory response to carbon dioxide is decreased in states of anoxemia.

The study of the relation of high oxygen tensions to the stimulating
effects of carbon dioxide has received little attention. In fact, most of the
investigations on carbon dioxide hyperpnea have been carried out without
regard to the concentration of oxygen inhaled, except that in most in-
stances anoxemia was avoided by using an "excess" of oxygen. To our
knowledge Yamada (16) was the first to recognize that the inhalation of
carbon dioxide-oxygen mixtures caused a greater respiratory increment
than did the inhalation of carbon dioxide mixed with air. His experi-
mental technique consisted of the measurements of alveolar carbon dioxide
tensions. Davies, Brow and Binger (4) reported similar results but since
"in some cases the percentage increase differed but little from the mean
deviation," they were unwilling to lay any stress on their findings and felt
that the matter could be decided definitely only "through statistical
methods based upon a large amount of data collected under carefully

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standardized conditions." In our own work an attempt has been made to clarify the effects of breathing several concentrations of carbon dioxide in pure oxygen and in 21 per cent oxygen by carefully controlled experiments with a larger number of subjects.

Experimental. Twenty-three male college students, ranging in age from 18 to 28 years, served as subjects. The number of subjects used for each concentration of carbon dioxide may be seen in table 2. Each subject was tested twice with a given carbon dioxide concentration in the presence of both 21 per cent oxygen and high oxygen. Each experiment consisted of 1, a period of 30 minutes during which the expired air was measured while the subject breathed outdoor air; 2, the test period during which the gas mixtures were breathed (this period was long enough for the respiratory volume to become stabilized), and 3, an after-period of 20 minutes during which the subject again breathed outdoor air. Each subject was tested at a uniform time of day and had not eaten for one hour prior to each test. A Siebe-Gorman half-mask was adjusted to each subject and the expired air was measured over a period of 20 minutes while the subject was in the supine position in order to assure stable values of respiratory volume (13). The expired air was collected in a pair of recording spirometers of the Tissot type, each with a capacity of 9.19 liters (S.T.P.). These operated continuously in alternation and recorded electrically when each tank was filled. Egg shell valves (floating on mercury and opened by a pressure of 1.5 mm. of water) separated the inspired and expired air. After four preliminary trial runs, each on a different day, the experimental series was begun. Each subject was tested with only one mixture on any single day, but the tests with a similar mixture were repeated on a succeeding day.

In order to eliminate any effect of practice, the test series was counter-
balanced by having one-half the subjects breathe the carbon dioxide-air mixtures first and the other half the carbon dioxide-oxygen mixture first.

The gas mixtures were obtained in four 6000-liter high pressure tanks from which a pair of Tissot spirometers, each with a capacity of 60 liters,

| TABLE 2 |
|---|---|---|---|
| Effect of O₂ content on increment in respiratory volume resulting from increasing CO₂ in inspired air |
| Percentage increment in respiratory volume (based on average resting respiratory volume for each subject during fore-period) |

<table>
<thead>
<tr>
<th>SUBJECT NUMBER</th>
<th>1% CO₂</th>
<th>2% CO₂</th>
<th>4% CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In 21% O₂</td>
<td>In 98% O₂</td>
<td>Diff.</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>61</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>42</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>30</td>
<td>22</td>
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<tr>
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<td>10</td>
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<td>13</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
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<td>20</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>31</td>
<td>0</td>
</tr>
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<td>13</td>
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<td>9</td>
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<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean...</td>
<td>14.2</td>
<td>28.4</td>
<td>14.2</td>
</tr>
<tr>
<td>S.M. diff...</td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.R...</td>
<td>4.7</td>
<td></td>
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</tr>
</tbody>
</table>

was filled. The use of these large Tissot spirometers allowed the gas mixtures to come to the same temperature and pressure as the air in the room before being respired. One of the large spirometers was filled from the storage tanks while the subject breathed the mixture from the other. The intake valves were arranged so that the mixtures could be connected
to the inspiratory circuit without the knowledge of the subject. The carbon dioxide content of the gas mixtures from the high pressure tanks and from the large Tissot spirometers was measured before each separate test and was found to vary less than ±0.04 per cent from the purported value.

Fig. 1. Effect of alterations in O₂ tension on increase in respiratory volume produced by low concentrations of CO₂ in inspired air in normal male. Ordinate—cumulative time in minutes required to expire equal units of air (9.11 l.). CO₂-O₂ mixtures administered over intervals between arrows. All 12 experiments on single subject age 23. Height 176.6. Weight 77.4. Curves 1 and 4 are duplicate experiments in which a mixture of 1 per cent CO₂, 21 per cent O₂, and 78 per cent N₂ was administered. In curves 2 and 5 a mixture of 1 per cent CO₂, 99 per cent O₂ was administered. In curves 6 and 8 a mixture of 2 per cent CO₂, 21 per cent O₂ and 77 per cent N₂ was administered. In curves 7 and 9 a mixture of 2 per cent CO₂ and 98 per cent O₂ was administered. In curves 10 and 11 a mixture of 4 per cent CO₂, 21 per cent O₂ and 75 per cent N₂ was administered. Experiments were run in the temporal order as numbered.

Analysis of data and results. Respiratory volumes were computed by dividing the volume of expired air in each 9.19 liter tank (corrected to 0°C and 760 mm. pressure) by the time required to fill each tank, and were recorded as volumes in liters per minute or as volumes in liters per square
meter per minute. In all the experiments the resting level was determined from an average of at least 10 observations following the 20-minute rest period. In order to decide which points should be included in the determination of the resting level, graphs were constructed (see fig. 1) in which cumulative time was plotted as the ordinate and the number of tanks filled with expired air was plotted as the abscissa. Straight lines were fitted by free-hand methods to the experimental points so plotted. As can be seen in figure 1, these points form a straight line when the respiratory volume is constant. Increases in respiratory volume result in a decrease in the slope of the line. Average values were computed using only points after a linear trend had been established. The resting level was used as the value from which all deviations caused by breathing the carbon dioxide mixtures were computed. Table 1 is a summary of average results from all the subjects calculated in per cent, together with the critical ratios (computed as ratio of the mean difference between resting respiratory volume and stimulated volume divided by the standard error of the difference). The increments in table 1 are based on the averages of two tests for each subject, with the baseline calculated on the fore-period.

Table 1 indicates that carbon dioxide mixed with 21 per cent oxygen causes a significant increase in the respiratory volume in all concentrations used. One per cent carbon dioxide causes a mean increase of approximately 14 per cent, while 2 per cent carbon dioxide causes an increase of about 34 per cent. We found, as have others, that 4 per cent carbon dioxide doubles the respiratory volume. On the other hand, when the same concentrations of carbon dioxide are mixed with pure oxygen, the increments are much greater. Thus, 1 per cent carbon dioxide in oxygen increases the respiratory volume almost as much as does 2 per cent carbon dioxide in air.

Since each subject breathed a given percentage of carbon dioxide in 21 per cent oxygen and also the same percentage of carbon dioxide mixed with pure oxygen, the significance of the difference in respiratory response to carbon dioxide under the two conditions was tested by the method of differences, as summarized in table 2. This table shows that the response to all concentrations of carbon dioxide mixed with pure oxygen is significantly greater than to the same concentrations of carbon dioxide mixed with 21 per cent oxygen, since the critical ratios are 4.7, 4.5 and 4.7 for 1, 2 and 4 per cent carbon dioxide.

DISCUSSION. A possible explanation of our results is that in the presence of a high oxygen tension in the respiratory center the sensitivity of these cells to the normal stimulus of increase in hydrogen ion concentration may

2 This method of plotting was utilized because fewer calculations were required and because this method tends to minimize the effects of chance fluctuations.
be enhanced so that respiration is increased without a measurable rise in the hydrogen ion concentration or in carbon dioxide of the center. It is true that if 13.3 per cent (the average increment in respiratory volume produced by breathing 100 per cent oxygen) is deducted from the values obtained when carbon dioxide mixed with pure oxygen is inspired (table 2), the discrepancy is 0.9 per cent \((14.2 - (28.4 - 13.3))\) when breathing 1 per cent carbon dioxide; 5.2 per cent \((34.3 - (52.8 - 13.3))\) when breathing 2 per cent carbon dioxide; and 16.6 per cent \((98.6 - (128.5 - 13.3))\) when breathing 4 per cent carbon dioxide. If these increasing differences were statistically significant, it would prove that the respiratory center is more sensitive to a given concentration of carbon dioxide when the oxygen tension is increased. However, the differences, although suggestive, are not statistically significant.

Since it has been shown previously that a significant rise in respiratory volume results from breathing 100 per cent oxygen (14) we are forced to conclude that the results observed represent only an additive effect of increased \(O_2\) tension and increased \(CO_2\) tension. Since the differential effect does not disappear with breathing 4 per cent \(CO_2\) we doubt whether it can be attributed to a reduction in blood flow in the brain which Lennox and Gibbs (8) and other investigators (10, 11) have found in humans and mammals breathing pure oxygen.

The rise in \(CO_2\) tension of the tissues of animals breathing pure oxygen reported by Campbell (2), as well as the rise in \(CO_2\) tension of both arterial and venous blood in animals breathing pure \(O_2\) at 4 atmospheres' pressure reported by Behnke, Shaw et al. (1), lend support to the thesis originally proposed by Gesell (6) that in the presence of high oxygen tension the transport of carbon dioxide from the tissues might be interfered with because the amount of reduced hemoglobin available to transport a given amount of \(CO_2\) would be reduced as a result of the increased amount of oxygen carried in physical solutions.

Practically, the conclusion to be drawn from our work is that a given concentration of carbon dioxide should be mixed with oxygen rather than with air to produce a maximal degree of hyperpnea. Conversely, (as concluded from the work of others), in states of anoxemia oxygen should be used in high concentration in order to enhance the respiratory response to either the carbon dioxide present or to the carbon dioxide that may be added.

**Summary.** A group of 31 adult males has been studied. Each subject rested for 30 minutes in order to stabilize the respiratory volumes and then breathed (through a Siebe-Gorman half-mask) a mixture of 1 per cent carbon dioxide and 21 per cent oxygen for a period of 8 to 15 minutes, after which time the respiratory volume was again stable but at a higher level. This experiment was repeated with 1 per cent carbon dioxide and 99 per
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In all the experiments the average increment in the respiratory volume was greater when the subject breathed 1 per cent carbon dioxide in 99 per cent oxygen than when he breathed 1 per cent carbon dioxide in 21 per cent oxygen. Similar results were obtained when 2 and 4 per cent carbon dioxide were mixed with oxygen. In some subjects the difference in respiratory response was great enough to be of clinical importance and should be considered when carbon dioxide is administered for therapeutic purposes.

CONCLUSIONS

1. Data are shown which give the average effect of 1, 2 and 4 per cent carbon dioxide on the respiration of normal adult males.

2. Normal subjects respond with a greater increment in respiratory volume to carbon dioxide (in concentrations of 1, 2 and 4 per cent) mixed with pure oxygen than to the same concentrations of carbon dioxide mixed with air.

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