Lung Volume Restriction, Hypoxia and Hypercapnia as Inter-related Respiratory Stimuli in Normal Man

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The stimulating effects of hypoxia and hypercapnia upon respiration have long been recognized and have been subjected to intensive study. Less attention has been given to the relationship of these stimuli to a third strong respiratory stimulus, namely, restricted inflation of the lungs. The following experiments were designed to evaluate the relative importance and interrelationships of hypoxia, hypercapnia and restricted lung volume in the voluntary control of respiration in normal subjects. The results indicate that these three factors have an additive effect in the production of the net respiratory stimulus. If the influence of restricted lung volume is removed by hyperinflation of the lungs, the net respiratory stimulus is reduced. Conversely, if the lungs are deflated, the net stimulation is increased.

METHODS

The experimental procedure described below was performed on 6 subjects aged 22-37 yr. The subject, seated in a straight chair and wearing a nose clip, quietly breathed room air through a rubber mouthpiece connected to a three-way valve. The instrumental dead space was 70 cc. On one arm of the valve was a rubber anesthesia bag containing 3, 1, 2, 4 or 9 liters of a gas mixture, the composition of which was unknown to the subject. After accommodating himself to the apparatus and at the end of a normal exhalation, he exhaled maximally and then turned the valve, thereby connecting himself with the rubber bag. He breathed as deeply as possible 18 times/min. at a rate set by a metronome. When he could no longer control his respirations at this level, he again exhaled maximally and turned the valve to trap the exhaled gas in the bag. The point in the procedure when the valve was thus turned back was called the breaking point of rebreathing. The time of rebreathing and any symptoms or physical signs that developed were noted. The gas in the bag was analyzed at once for oxygen and carbon dioxide and its volume measured in a calibrated 9-liter spirometer. This volume, when it did not exceed the vital capacity, was a measure of the extent of lung inflation and with the residual air constituted the total lung volume. When using the 9-liter bag, its final volume exceeded the subjects’ vital capacity; therefore the final lung volume was taken to be the vital capacity at a respiratory rate of 18/min. All volumes were converted to B.T.P.S. The partial pressures of oxygen (pO₂) and of carbon dioxide (pCO₂) found were used as measures of hypoxia and hypercapnia, respectively.

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Some of the experiments were preceded by a period of 1–2 min. of hyperventilation in order to lower the alveolar CO₂ tension initially. The respiratory stimulus from change in blood pH was not varied independently from that of pCO₂.

Gas analyses were performed with water-jacketed Scholander quick gas analyzers (1, 2) with indigo carmine as an indicator (3). Analyzers and syringes were calibrated with mercury and water, respectively, and checked daily using outside air as a standard. The air analyses had a standard deviation of ±0.3 volume%.

These procedures were repeated on each subject using different initial gas mixtures and initial bag volumes from 0.5–9 liters (table I). The order in which the procedures were performed was determined for each subject from a table of random numbers. Residual air volumes were measured on 4 of the subjects by a rebreathing method (4).

**Table I. Initial gas compositions and volumes of the rebreathing bag in a typical experiment on one subject**

<table>
<thead>
<tr>
<th>Initial Bag Vol.</th>
<th>Air</th>
<th>O₂</th>
<th>N₂</th>
<th>O₂ + 5% CO₂</th>
<th>50% Air + 50% O₂</th>
<th>25% Air + 75% O₂</th>
<th>75% Air + 25% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>18</td>
<td>27</td>
<td>15</td>
<td>22</td>
<td>2</td>
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<td>14</td>
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<td>24</td>
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<td>19</td>
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<td>2</td>
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<td>23</td>
<td>34</td>
<td>9</td>
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<tr>
<td>4</td>
<td>13</td>
<td>30</td>
<td>7</td>
<td>31</td>
<td>35</td>
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</tr>
<tr>
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<td>26</td>
<td>29</td>
<td>11</td>
<td>20</td>
<td>5</td>
<td>28</td>
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</tbody>
</table>

The numbers represent the random order in which the procedures were performed.

**Results**

The relation between restricted lung inflation, pO₂ and pCO₂ in determining the breaking point of rebreathing is illustrated in the figure which is a plot of the data for the one subject on whom the most procedures were performed (subject J.C.M.). Similar relationships were found in the other 5 subjects on whom 195 procedures were performed. Lack of space prevents publication of these results.

The upper curve illustrates the determination of breaking points through the interaction of oxygen and carbon dioxide tension in the absence of restricted lung inflation. When inflation of the lung was restricted by reduction in volume of the rebreathing bag, uncontrollable stimulation to breathe occurred with less hypoxia and less hypercapnia in the manner shown. Occasionally when anoxia was present without hypercapnia or restricted lung inflation (e.g. at the lowest point on the upper curve) marked cyanosis, loss of consciousness and convulsions occurred before stimulation of breathing was strong enough to produce a breaking point.

When hypercapnia without hypoxia or restricted lung inflation determined the breaking point (e.g. the point at 550 mm pO₂ on the upper curve), the subject felt excessive warmth and vertigo and disorientation were noted. Occasionally the bag had to be forcibly taken from him although he was still able to keep his respiratory

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2 Detailed data have been deposited with the American Documentation Institute, Library of Congress, Washington 25, D. C. For copies of these order Document 3980 directly from the Institute, remitting $1.25 for microfilm (images 1 inch high on 35-mm film) or $1.25 for photostat readable without optical aid.
rate down to that set by the metronome. When restricted lung inflation, hypoxia and hypercapnia were present simultaneously, no loss of consciousness occurred and the breaking points were more definite.

The time of rebreathing was not an independent variable in the production of respiratory stimulus. Many points lying close together are from experiments which started from different initial gas mixtures, but which reached similar $pO_2$, $pCO_2$ and volumes at the breaking points in different lengths of time. No significant day to day variation in breaking points was observed for any one subject.

The pulmonary residual air volumes on 4 of the subjects were as follows: subject J.C.M., 1409 cc; subject C.D.S., 2135 cc; subject H.E.P., 1909 cc; subject S.U., 1066 cc.

**FIG. 1.** Relation between $pO_2$, $pCO_2$ and volume of gas in rebreathing bag at breaking point. Each point represents 1 rebreathing procedure; all are from experiments on 1 subject (J.C.M.). Curves are drawn through points of equal volume.

**DISCUSSION**

In 1908, Hill and Flack (5) showed that the absence of hypoxia increases the tolerance for carbon dioxide during breath holding. Somewhat later, Haldane (6), studying the apnea which follows forced breathing, further clarified this relationship by extending the range of oxygen tensions studied. The curve he obtained, showing the increased tolerance for carbon dioxide which accompanies increasing tensions of oxygen, is similar to those recently derived by Ferris et al. from arterial blood (7) and by Rahn and Fenn from alveolar air (8). Ferris et al. stressed the fact that increasing tensions of oxygen allow for increasing tolerance for carbon dioxide only until the partial pressure of oxygen reaches approximately 100 mm Hg. These studies were all done without controlled variation in lung volume.

In animal experiments it has been demonstrated that reflex control of respiration is effected by afferent stimuli from the lungs, larynx, trachea, aorta etc. Two Hering-Breuer reflexes, both mediated through afferent vagal channels, have opposing effects. One, brought about by stimuli arising from stretch receptors in the lungs, causes depression of centrally induced inspiration (9-15). The other, brought about by withdrawal of air from the lungs with resulting deflation, causes stimulation of centrally induced inspiration (13, 16). The afferent vagal discharge for both of these reflexes is dependent upon lung volume and independent of respiratory movement (13-14).
In another type of animal experimentation, it has been shown that, if the vagi are intact, stimulation of respiration occurs when expansion of the lungs is restricted either by making external pressure upon the thorax (17–19), or by the technique of negative pressure breathing (20).

The relation between the volume of gas in the lungs and the maximum breath-holding time has been studied in man as a method of determining residual air (21–24). In the earlier studies of Monod and Cara (21) and Vacca and Boeri (22, 23) the maximum breath-holding time was shown to be a function of the total gas volume in the lungs, but this effect of volume was confounded with the chemical stimuli from hypoxia and hypercapnia which were not measured. Muxworthy (24) included alveolar gas analyses in his study of the effect of lung volume on maximum breath-holding time; his data suggest the existence of a respiratory stimulus from lung volume restriction.

In the light of the observations on animals, it has been concluded that both of the Hering-Breuer reflexes were active in our experiments. Lung inflation depressed, lung deflation stimulated breathing. Hypercapnia could be tolerated to the point of anesthesia, if the subject had a large volume of oxygen to rebreathe. Similarly, hypoxia could be better tolerated if the anoxic gas mixture was of large volume.

In the case of reflex stimulation, the strength of the stimulus increased exponentially from maximum depression at the position of complete inflation of the lungs to maximum stimulation at the position of forced expiration. Hyperinflation of the lungs was strongly inhibitory. These observations are consistent with the view that there are two opposing afferent reflex receptors for physical stimuli. In contrast, the effect of the chemical stimuli appeared to be rather one-sided. Hypocapnia and hyperoxia were only weakly inhibitory. The strength of the CO₂ stimulus increased exponentially from hypocapnia to a maximum at lung CO₂ pressures of about 80 mm Hg. Higher concentrations induced anesthesia and respiratory depression. The strength of the O₂ stimulus increased exponentially from hyperoxia to a maximum stimulation at lung O₂ pressures of 20 to 25 mm. Lower oxygen tensions induced unconsciousness without strongly stimulating respiration. The net response of the respiratory mechanism results from integration of the separate physical and chemical stimuli.

The question arises as to whether the effects attributed to the Hering-Breuer reflexes were actually due to changes in gas tensions in the arterial blood, which might have been detected if blood gas analyses had been carried out. Intrapulmonary mixing of gases occurs rapidly in normal subjects who breathe maximally every few seconds. After a few breaths, the difference between O₂, CO₂ and N₂ tensions in arterial blood and in mixed lung gas is at most a few millimeters of mercury (25). In our experiments where lung volume was unrestricted, the data in respect to the pO₂ and pCO₂ relationship of bag gas agree with data obtained by others from arterial blood and alveolar gas during breath holding (7, 8). This is additional evidence of near-equilibrium of the bag-lung system at the breaking point of rebreathing.

The experimental design resulted in two volume variables which are confounded. One of these was the tidal volume during rebreathing which, since the subject was asked to breathe at maximal possible depth, varied with different procedures from 300 cc to the vital capacity. The other variable was the total volume of gas in the lungs independent of the tidal volume. Experiments are in progress to separate
these 2 variables and to evaluate their individual roles in the production of the reflex respiratory stimulus.

The manner and rate of change in $pO_2$ differed from that in $pCO_2$ during rebreathing. The $pO_2$ decreased more rapidly the smaller the bag, since the $O_2$ consumption was nearly the same regardless of volume. During rebreathing the rate of change in $pO_2$ remained fixed. The $pCO_2$, on the other hand, increased sharply during the first few breaths, then slowly as the $CO_2$ output into the lungs fell. The time required for this change in $CO_2$ output was longer the larger the volume of the bag.

These rates of change in composition of the bag gases are in some instances of importance in respect to the gas tensions at the breaking point. If one considers the circulation time from lung to medullary respiratory center, the $pCO_2$ in the arterial blood, which was actually responsible for stimulation, was that existing in the lung-bag system approximately 10 sec. before the breaking point. Similarly, the stimulus of hypoxia was that of the $pO_2$ existing in the lung-bag system shortly before the breaking point. In most of the experiments the slow rate of change of $pCO_2$ near the breaking point, and the short time lag with respect to $pO_2$ make any correction for these factors unnecessary. In procedures where the rebreathing time was 30 sec. or less, however, the $pCO_2$ and $pO_2$ were both changing rapidly. If it were possible to make a correction for circulation time, such a correction would increase the apparent effect of lung volume restriction as a stimulus by displacing the lower curves in the figure downward and to the right.

A review of the literature on the subject of respiratory control reveals the recognition by several investigators of reflex respiratory stimuli from the lungs which are dependent upon lung volume. These previous studies, however, have not included the relationship between these reflexes and the chemical stimuli from hypoxia and hypercapnia. We have shown that the reflex stimuli from restriction in the volume of lung gas and the inhibition of breathing by lung inflation are interrelated with the chemical stimuli from hypoxia and hypercapnia. These interrelations should be included in the integrated concept of respiratory control.

**SUMMARY**

This work emphasizes a seldom recognized relationship between the reflex respiratory stimuli dependent upon lung volume and the chemical stimuli from hypoxia and hypercapnia. These reflexes, presumably originating in stretch receptors in the lungs, are here brought into a quantitative relation with the stimuli from hypoxia and hypercapnia.

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**REFERENCES**