This relationship between phrenic inhibition and lung volume may relate to the input-output characteristics of the inspiratory terminating mechanism, and the abrupt downstroke in the phrenic neurogram, commonly taken to signify the end of inspiration, may represent simply an extension of the alinear function. Also, because the vertical distances between iso-inhibition lines change little with inspiratory time, the shape of the inhibition-volume relationship is similar at various inspiratory times. This presumably signifies constant properties of the inspiratory terminating mechanism, independent of time after onset of inspiration. The level of phrenic efferent discharge does not consistently correlate with the volume threshold for I-E transition, and when efferent activity is constant during the plateau phase of an apneustic breath, the threshold continues to fall with time. These observations indicate that the fall in volume threshold is not strictly related to central inspiratory activity. If the two are at all related, the relationship must be time-dependent.

REFERENCES

A New Analysis of the Interaction of Hypoxia and Hypercapnia on Breathing*

Etsuro K. Motoyama, M.D.; José J. Almirall, M.D.; and Joseph Milic-Emili, M.D.

The effect on the control of breathing of hypoxia, hypercapnia and their interaction has been investigated extensively since the classic studies by Haldane and Priestley.1 In most studies, the effect of hypoxia on the respiratory response to CO₂ was assessed by measuring the ventilation (V) assuming that it reflects the respiratory center's output. Barcroft and Margaria1 and more recently Clark and von Euler have suggested that the rate of rise of inspiratory volume or the mean inspiratory flow rate, obtained by dividing the tidal volume by duration of inspiration (VT/T₁), might be a better index of neural inspiratory drive. As recently described, the relation between V and VT/T₁ is given by:

\[ V = (V_T/T₁) \times (T₁/T₆0) \] (1)

where T₁/T₆0 is the "duty cycle" of the inspiratory muscles, i.e., it indicates the fraction of the respiratory cycle spent in inspiration.

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cycle when the inspiratory muscles are active. With this approach ventilatory response to respiratory stimulants or depressants can be analyzed in terms of inspiratory drive and effective timing ratio.

The present study was undertaken to reassess the respiratory response to hypoxia and hypercapnia using the new analytical approach.

METHODS

Healthy volunteers (men) were studied. Prior to the experiment, the procedures and the possible risks involved were explained to their satisfaction and written consent was obtained. Cylinders containing 100% oxygen, nitrogen and carbon dioxide with reducing valves were connected through a common tube to a humidifier which also served as a mixing chamber.

The subject breathed a gas mixture through a non-rebreathing valve system with a pneumotachograph.

Measurements were made with the patient in the supine position, since previous studies\(^7,8\) have shown that in this position functional residual capacity (FRC) does not change appreciably during \(\text{CO}_2\) rebreathing, while it decreases in sitting position; such changes in FRC would make the interpretation of the results more difficult. At a constant FRC, on the other hand, the rate of rise in phrenic activity has been found in cats to reflect the rate of rise in lung volume.\(^9\)

Ventilation was measured during the steady state breathing of 50% oxygen, room air and 3 levels of hypoxic mixtures. The inspired concentration of \(\text{CO}_2\) was varied at 3-4 different levels for each level of oxygen and was maintained for at least 5 minutes before the measurement of respiratory response was made. The vital capacity (VC) and expiratory reserve volume (ERV) were measured in each run. Flow, volume, alveolar (end-tidal) \(\text{O}_2\) and \(\text{CO}_2\) concentrations, as well as the electrocardiograph, were continuously monitored and recorded. In this report, the data dealing with normoxic hypercapnia and hypoxia (\(\text{FiCO}_2 = 0\)) in two representative subjects are presented.

RESULTS AND DISCUSSION

In supine position, both VC and ERV changed little while \(\dot{V}\) changed markedly with hypercapnia and hypoxia.

As the alveolar \(\text{Pco}_2\) was increased by 10 mm Hg from room air control, there was a steady increase in ventilation in most of the subjects studied, but the slope of the ventilatory response to \(\text{CO}_2\) (\(\Delta V/\Delta \text{Paco}_2\)) varied considerably from one subject to the other. Table 1 compares the data of the two subjects. Ventilatory response to \(\text{CO}_2\) was higher in subject 1 than in subject 2. In terms of the mean inspiratory flow, however, the difference between the 2 was negligible. This discrepancy between ventilatory and \(\dot{V}\)/\(T_i\) response to \(\text{CO}_2\) was due to the difference in \(T_i/\text{TOT}\) response between the two subjects. In subject 2, the increase in \(\dot{V}\) was entirely due to an increase in \(T_i/\text{TOT}\) since \(T_i/\text{TOT}\) did not change. In subject 1, on the contrary, \(T_i/\text{TOT}\) increased from 0.40 to 0.52 and hence, as expected from equation (1), the \(\Delta V\) response was greater than that in subject 2.

In subject 1, the increase in \(T_i/\text{TOT}\) with hypercapnia was due to a shortening of expiratory time (\(T_e\)) as \(\text{Paco}_2\) was increased while \(T_i\) remained essentially unchanged. This observation is in agreement with the findings of Cunningham and Gardner in man.\(^8\) In subject 2, both \(T_i\) and \(T_e\) decreased somewhat as \(\dot{V}\) increased, but by the same proportions so that \(T_i/\text{TOT}\) remained constant.

Table 2 shows the data from the same subjects in response to hypoxia. As \(\text{PAO}_2\) was decreased from room air control to 42 mm Hg, \(\dot{V}\) and \(\dot{V}/T_i\) increased in both subjects. Subject 1 showed a higher ventilatory response.
Table 1—Changes in $\dot{V}$, VT/Ti and Ti/TTOT when PACO$_2$ was Increased by 10 mm Hg Above Room Air Control

<table>
<thead>
<tr>
<th>Subject</th>
<th>$\Delta \dot{V}$ (L/min)</th>
<th>$\Delta V_T/T_i$ (L/min)</th>
<th>$\Delta T_i/T_{TOT}$</th>
<th>$\Delta V_T$ (L)</th>
<th>$\Delta f$ (cpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.1</td>
<td>34.9</td>
<td>0.12</td>
<td>.96</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>16.1</td>
<td>34.8</td>
<td>0.02</td>
<td>.81</td>
<td>1.9</td>
</tr>
</tbody>
</table>

than subject 2. The hypoxic V$_T$/Ti response, however, was similar in the 2 subjects. As in the case of the hypercapnia experiments, the greater ventilatory response to hypoxia in subject 1 was due to the fact that in this individual Ti/T$_{TOT}$ increased (from 0.40 to 0.49), while in subject 2 it remained unchanged.

In subject 1 the hypoxic increase in Ti/T$_{TOT}$ was achieved by a disproportional shortening of Ts in comparison to Ti while V$_T$ increased only slightly. In subject 2, on the other hand, both Ti and Ts were shortened proportionally so that the Ti/T$_{TOT}$ ratio was unaffected. In this connection it should be noted that in both subjects hypoxia and hypercapnia caused an increase in f, but their effect on Ti/T$_{TOT}$ was markedly different.

The contribution of changes in VT/Ti and Ti/T$_{TOT}$ to the ventilatory response to various stimuli can be assessed graphically by plotting V against V$_T$/Ti. Figure 1 illustrates such an analysis pertaining to the data on the effect of hypercapnia in the 2 subjects.

In Figure 1a (subject 2) both experimental points A (room air control) and B (PaCO$_2$ = 49 mm Hg) lie on a linear function starting at the origin of the graph (V = k $\times$ V$_T$/Ti). According to equation (1), the slope k of the function represents a constant Ti/T$_{TOT}$ value of 0.43. Thus, in this subject there is no change in Ti/T$_{TOT}$ as V$_T$/Ti increases with hypercapnia, and consequently the increase in V is solely due to the increase in V$_T$/Ti.

In Figure 1b (subject 1) the dotted lines radiating from the origin represent two different Ti/T$_{TOT}$ isopleths, amounting to 0.40 and 0.52, respectively. In this individual, the experimental point A (room air control) lies on the Ti/T$_{TOT}$ isopleth of 0.40. As PaCO$_2$ increases, both V$_T$/Ti and Ti/T$_{TOT}$ increase, as shown by the experimental point B (PaCO$_2$ = 50 mm Hg) which lies on the Ti/T$_{TOT}$ isopleth of 0.52. Of the total increase in V (D,B) in response to hypercapnia, approximately 70% (D,C) is due to the increase in V$_T$/Ti while the remaining 30% (C,B) is attributable to the increase in Ti/T$_{TOT}$. In this analysis point C represents the V that would obtain if Ti/T$_{TOT}$ had not increased with hypercapnia.

A similar analysis on the hypoxia data of subject 1 revealed that the increased Ti/T$_{TOT}$ accounted for approximately 50% $\Delta V$ in contrast to 30% during hypoxia in subject 2.

Table 2—Changes in $\dot{V}$, VT/Ti and Ti/TTOT when PAcO$_2$ was Decreased to 42 mm Hg from Room Air Control (FICO$_2$ = 0)

<table>
<thead>
<tr>
<th>Subject</th>
<th>$\Delta \dot{V}$ (L/min)</th>
<th>$\Delta V_T/T_i$ (L/min)</th>
<th>$\Delta T_i/T_{TOT}$</th>
<th>$\Delta V_T$ (L)</th>
<th>$\Delta f$ (cpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.5</td>
<td>5.6</td>
<td>0.09</td>
<td>.33</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>2.7</td>
<td>5.4</td>
<td>0.01</td>
<td>.04</td>
<td>3.3</td>
</tr>
</tbody>
</table>

capnia in spite of the fact that during hypoxia the increase in Ti/T$_{TOT}$ was less than during hypercapnia (Tables 1 and 2). This difference in Ti/T$_{TOT}$ contribution to $\Delta V$ is due to the fact that during hypoxia the Ti/T$_{TOT}$ increase per unit increase in ventilation was much greater than during hypercapnia.

These findings indicate that the measurement of ventilatory response has limitations as an index of inspiratory drive. Partitioning of ventilation into mean inspiratory flow and Ti/T$_{TOT}$, as described above, provides more direct information concerning inspiratory drive, and allows assessment of the contribution of the duration of the respiratory phases to ventilation.

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1 Haldane JS, Priestley JG: The regulation of the lung ventilation. J Physiol (London) 32:225, 1905

DISCUSSION

Dr. Cameron: When you do your hypocapnic perfusion, would another possibility for the change in recovery be that alkaline perfusion of the central chemoreceptor areas increases carotid sinus nerve efferent activity and therefore decreases carotid sinus nerve afferent activity? In other words, a central alkalosis could turn off the peripheral receptor.

Dr. Grunstein: Dr. Edelman, do you see periodic breathing with low cerebral blood flow?

Dr. Edelman: No. We are trying to repeat the old studies of Guyton and put in a delayed flow circuit. This turns out to be difficult because if you just use long tubing you not only delay flow, but also decrease it. But with low flow we haven’t seen cycling.

Dr. Eldridge: I’d like to make a few comments about Dr. Dutton’s conclusions that chemical factors may dominate neural factors. It’s clear that regardless of what else is going on, if you lower the CO$_2$ level you are going to lower the overall input stimulus and you’re going to
lower output, so your findings do not in any way negate this neural mechanism which decays slowly.

**Dr. Dutton:** I agree. However, the time constants of the reverberations that you showed were something like 45 seconds. The time constants in our study for all 3 types of flow were higher than 175 seconds for ventilation and for tidal volume they're all higher than 250 seconds. For frequency, of course, they are very high, so that in any one of these conditions we are not approaching the kind of time constant that you describe as a purely neural reverberation mechanism.

**Dr. Eldridge:** Probably both neural and chemical factors contribute.

**Dr. Edelman:** Dr. Dutton, I have a question. In this preparation you're setting up a large gradient between cortical PCO₂ and brain stem PCO₂. That might produce a time constant due to the flux of CO₂ through the brain. Now if that's true, I don't see that your time constants, although real, can be interpreted in the physiologic sense.

**Dr. Dempsey:** Dr. Cotton, is the decrease in ventilation with hypoxia in your babies true hypventilation or does metabolic rate fall in these babies rather easily? That is, is ventilation simply following metabolic rate?

**Dr. Cotton:** I don't know. I don't think that's ever been measured.

**Dr. Eldridge:** This study demonstrates some of the problems using ventilation in response to a change in the gas which is given and trying to make any conclusion as to what's doing it. It seems to me that some of those changes that you showed at the beginning of giving high oxygen could very well be a change in the timing of the appearance of an oscillation at the carotid body.

**Dr. Edelman:** Do we know whether or not the depression of ventilation is due to brain hypoxia? In children with familial dysautonomia you see exactly the same pattern—hyperventilation followed by hypoventilation. If you measure their blood pressure you see that it has fallen enough to probably decrease brain blood flow.

**Dr. Cotton:** In these babies, blood pressure stays constant and heart rate stays constant, but I agree that brain blood flow may be the deciding element.

**INTRAPULMONARY AND NEUROMUSCULAR RECEPTOR FACTORS**

**Respiratory Muscle Function in Amyotrophic Lateral Sclerosis**

Stephen M. Kreitzer, M.D.; Nicholas A. Saunders, M.D.; H. Richard Tyler, M.D.; and Roland H. Ingram, Jr., M.D.

Patients with neuromuscular disorders often exhibit an unhalting progression in paralysis and die from respiratory failure, yet how respiratory muscle weakness contributes to abnormal pulmonary function remains poorly defined.

We studied the relationships between lung volume, flow and intrathoracic pressure in 32 patients with amyotrophic lateral sclerosis (ALS), who had a large range of respiratory muscle weakness. Total lung capacity (TLC) and its subdivisions were measured by plethysmography or helium dilution. Specific conductance, dynamic compliance and static deflation pressure-volume curves of the lung were measured by standard techniques. Maximum expiratory flow-volume curves were obtained spirometrically. Respiratory muscle function was assessed in two ways: first, mouth pressure was measured during maximal static inspiratory (MIPS) and expiratory (MEPS) efforts at least 4 lung volumes: total lung capacity, residual volume, functional residual capacity, and approximately 1 inspiratory capacity. Second, transdiaphragmatic pressure was measured in 9 patients able to swallow both esophageal and gastric balloons.

Among the 32 patients studied, total lung capacity was normal (97.69 ± 2.61% predicted, mean ± SEM)

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