The Mechanics of Breathing and Stabilization of Ventilation in Patients With Unilateral Cerebral Infarction

BY SAMUEL M. MCMAHON, M.D., AND ALBERT HEYMAN, M.D.

Abstract:

The mechanics of breathing and responses of the respiratory system to CO₂ during resistance breathing were studied in 12 patients with clinical evidence of unilateral cerebral infarction and compared with the findings in normal subjects. The respiratory abnormalities in patients with cerebrovascular disease consisted of noncompliant lungs and high levels of elastic and nonelastic work while rebreathing CO₂. There were no differences in responses of minute ventilation to CO₂ in the two groups. Unlike normal subjects, the patients did not increase their level of respiratory work to compensate for the addition of a modest external resistance to airflow, and the ventilatory response to CO₂ consequently, became less than in the normal subjects. This failure to maintain tidal volumes and minute ventilation while breathing through an external resistance may account for some instances of respiratory deterioration among patients with cerebrovascular disease.

Additional Key Words: noncompliant lungs, brain scan, hemiplegia, dysphasia, intrapulmonary exchange of respiratory gases.

Introduction

Although ischemic lesions of the medulla and brain stem are often associated with abnormalities in the control of respiration, small unilateral infarcts of the cerebral hemispheres are generally considered to have little effect on the regulatory mechanisms of respiration. Most studies of respiratory function in patients with stroke have reported alterations in arterial blood gases, minute ventilation or the ventilatory response to carbon dioxide. There are, however, no data concerning the effect of cerebral infarction on ventilatory mechanics or on the mechanical work performed by inspiratory muscles of respiration, despite the fact that respiratory work reflects the output of the respiratory center more accurately than does minute ventilation. The present study describes abnormalities in the mechanics of breathing, the intrapulmonary exchange of respiratory gases, and the stabilization of minute volume during resistance breathing in patients with unilateral cerebrovascular infarction.

Methods

Studies of respiratory function were made in 12 patients with clinical evidence for unilateral cerebral infarction caused by thrombosis of intracranial or extracranial cerebral arteries (table 1). All but one of the patients (Case No. 11) were studied within 11 days after the onset of their cerebrovascular episode. Eight of the patients were fully conscious and alert. The remaining patients (Case Nos. 2, 7, 11, and 12) were lethargic and somewhat disoriented but cooperative. Neurological deficits were present in each patient and consisted primarily of hemiplegia or dysphasia. The clinical diagnosis of unilateral infarction of the cerebral hemisphere was able to be confirmed in half of the patients by brain scan, electroencephalographical or angiographical examinations (table 1). Respiratory abnormalities in these patients were not clinically apparent and none of them had previous historical evidence of chronic obstructive pulmonary disease.

Thirteen young, healthy subjects and four elderly normal subjects were studied to establish normal values for the tests of respiratory function and for comparison with our findings in the patients (table 2). None of the normal subjects had current symptoms of respiratory disease. One subject smoked cigarettes (Case No. 1) and another (Case No. 5) smoked a pipe, but neither had smoked within 24 hours prior to the study. The clinical spirometric findings and the usual tests of ventilatory mechanics in these subjects were within normal limits (table 2). Only one (Case No. 1) had participated previously in studies of ventilatory mechanics and was familiar with the experimental equipment and procedures.

The tests of respiratory function which were chosen for this study were easily carried out by the patients with stroke even though some of them were lethargic at the time of the
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The ventilatory response to CO\textsubscript{2} was evaluated by a modification of the rebreathing technique of Clark and Read.\textsuperscript{9,10} After an initial equilibration period of three to five minutes breathing 35\% oxygen through a mouthpiece, the subject rebreathed from a 6-liter meteorological balloon containing 7\% CO\textsubscript{2}, 35\% O\textsubscript{2} and 58\% N\textsubscript{2} (fig. 1). Respiratory

TABLE 1
Baseline Arterial Blood Gas Analysis and Clinical Data in Patients With Unilateral Cerebral Infarction

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>Clinical data</th>
<th>Laboratory confirmation</th>
<th>PaO\textsubscript{2}</th>
<th>PaCO\textsubscript{2}</th>
<th>pH \textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58/M</td>
<td>Left hemiparesis of seven days' duration</td>
<td>EEG: slow waves right hemisphere Brain scan: abnormal perfusion over right hemisphere</td>
<td>67</td>
<td>38</td>
<td>7.47</td>
</tr>
<tr>
<td>2</td>
<td>62/M</td>
<td>Left hemiparesis of 11 days' duration</td>
<td>Brain scan: increased tracer uptake right hemisphere Arteriography: occlusion of right middle cerebral artery</td>
<td>64</td>
<td>31</td>
<td>7.42</td>
</tr>
<tr>
<td>3</td>
<td>75/F</td>
<td>Very mild left hemiparesis of ten days’ duration</td>
<td>EEG: slow waves bilaterally Brain scan: negative on two examinations</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>59/F</td>
<td>Aphasia and severe right hemiparesis of eight days' duration</td>
<td>EEG: normal Brain scan: negative Rapid sequence brain scan: abnormal uptake on left</td>
<td>83</td>
<td>34</td>
<td>7.49</td>
</tr>
<tr>
<td>5</td>
<td>51/M</td>
<td>Right hemiparesis and dysphasia of nine days' duration</td>
<td>EEG: normal Brain scan: negative</td>
<td>58</td>
<td>43</td>
<td>7.40</td>
</tr>
<tr>
<td>6</td>
<td>55/M</td>
<td>Right hemiparesis and numbness of six days' duration. Two episodes, five months and six years earlier</td>
<td>EEG: normal Brain scan: negative</td>
<td>81</td>
<td>33</td>
<td>7.43</td>
</tr>
<tr>
<td>7</td>
<td>38/M</td>
<td>Left hemiparesis with altered consciousness, six days' duration. Died one month later with contralateral stroke. Necropsy showed bilateral cerebral infarction</td>
<td>EEG: suppression over right hemisphere Initial arteriography: occlusion of right internal carotid artery Brain scan: increased uptake in right posterior parietal region</td>
<td>90</td>
<td>36</td>
<td>7.39</td>
</tr>
<tr>
<td>8</td>
<td>62/M</td>
<td>Left hemiparesis, six days' duration. Metastatic carcinoma of liver. Cerebrovascular disease uncertain</td>
<td>Brain scan: negative</td>
<td>58</td>
<td>31</td>
<td>7.49</td>
</tr>
<tr>
<td>9</td>
<td>72/M</td>
<td>Right hemiparesis, two days' duration. Three previous ischemic episodes over three years</td>
<td>Brain scan: negative</td>
<td>58</td>
<td>31</td>
<td>7.49</td>
</tr>
<tr>
<td>10</td>
<td>53/M</td>
<td>Right hemiparesis and aphasia, six days' duration</td>
<td>EEG: slow waves, left hemisphere Brain scan: increased uptake in left posterior parietal area Angiography: 30% to 50% stenosis of both internal carotid arteries</td>
<td>61</td>
<td>37</td>
<td>7.40</td>
</tr>
<tr>
<td>11</td>
<td>65/F</td>
<td>Left hemiparesis and dementia of two months' duration</td>
<td>Brain scan: increased uptake in right frontal area Angiography: occlusion of right anterior cerebral artery and ascending branches of right middle cerebral artery</td>
<td>81</td>
<td>40</td>
<td>7.41</td>
</tr>
</tbody>
</table>

Mean standard error

Arterial blood gases were drawn while the patient breathed ambient air.
### TABLE 2

**Normal Subjects, Pulmonary Function Data**

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Age/sex</th>
<th>FVC* liters BTPS</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC, %</th>
<th>PEFR liters/sec BTPS</th>
<th>Cl dyn liter/cm H&lt;sub&gt;2&lt;/sub&gt;O</th>
<th>MER cm H&lt;sub&gt;2&lt;/sub&gt;O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35/M</td>
<td>4.05</td>
<td>85.2</td>
<td>8.33</td>
<td>0.29</td>
<td>-15.</td>
</tr>
<tr>
<td>2</td>
<td>25/F</td>
<td>3.70</td>
<td>83.8</td>
<td>6.25</td>
<td>0.24</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>23/M</td>
<td>6.20</td>
<td>70.5</td>
<td>-</td>
<td>0.19</td>
<td>-19.</td>
</tr>
<tr>
<td>4</td>
<td>23/M</td>
<td>7.84</td>
<td>80.7</td>
<td>-</td>
<td>0.29</td>
<td>-24.</td>
</tr>
<tr>
<td>5</td>
<td>21/F</td>
<td>4.35</td>
<td>78.6</td>
<td>-</td>
<td>0.24</td>
<td>-26.</td>
</tr>
<tr>
<td>6</td>
<td>16/F</td>
<td>3.45</td>
<td>84.1</td>
<td>5.55</td>
<td>0.22</td>
<td>-20.</td>
</tr>
<tr>
<td>7</td>
<td>23/M</td>
<td>5.26</td>
<td>87.6</td>
<td>-</td>
<td>0.17</td>
<td>-29.</td>
</tr>
<tr>
<td>8</td>
<td>18/F</td>
<td>3.25</td>
<td>83.1</td>
<td>6.75</td>
<td>0.12</td>
<td>-23.</td>
</tr>
<tr>
<td>9</td>
<td>28/M</td>
<td>5.00</td>
<td>72.0</td>
<td>8.05</td>
<td>0.19</td>
<td>-17.</td>
</tr>
<tr>
<td>10</td>
<td>34/M</td>
<td>5.10</td>
<td>91.0</td>
<td>12.50</td>
<td>0.32</td>
<td>-22.</td>
</tr>
<tr>
<td>11</td>
<td>25/M</td>
<td>6.00</td>
<td>75.5</td>
<td>8.35</td>
<td>0.27</td>
<td>-21.</td>
</tr>
<tr>
<td>12</td>
<td>31/M</td>
<td>5.66</td>
<td>76.0</td>
<td>11.10</td>
<td>0.26</td>
<td>-19.</td>
</tr>
<tr>
<td>13</td>
<td>26/M</td>
<td>7.28</td>
<td>81.7</td>
<td>11.51</td>
<td>0.31</td>
<td>-20.</td>
</tr>
<tr>
<td>14</td>
<td>68/F</td>
<td>3.61</td>
<td>81.7</td>
<td>7.71</td>
<td>0.29</td>
<td>-14.</td>
</tr>
<tr>
<td>15</td>
<td>58/F</td>
<td>3.30</td>
<td>82.1</td>
<td>7.57</td>
<td>0.14</td>
<td>-20.</td>
</tr>
<tr>
<td>16</td>
<td>51/F</td>
<td>4.02</td>
<td>80.3</td>
<td>8.19</td>
<td>0.29</td>
<td>-14.</td>
</tr>
<tr>
<td>17</td>
<td>75/M</td>
<td>4.74</td>
<td>78.9</td>
<td>10.60</td>
<td>0.22</td>
<td>-23.</td>
</tr>
</tbody>
</table>

*FVC: Forced vital capacity.*

FEV<sub>1</sub>: Forced expiratory volume in one second.

PEFR: Peak expiratory flow rate.

Cl dyn: Dynamic lung compliance.

MER: Maximal pulmonary elastic recoil at total lung capacity.

SEM: Standard error of the mean.

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Volume changes were measured directly from a spirometer and an electrical signal proportional to volume was obtained from a potentiometer attached to the pulley of the spirometer.

The frequency response of the system was tested in two ways. When the response to a stepwise change of one liter was tested using the analysis of Fry, a linear amplitude response differing less than 5% from the actual volume change would be predicted with frequencies less than 4.2 Hz. The system was also driven with a 1-liter sinusoidal wave from a Mueller-Morch respirator, and the resultant volume change was compared with a Fleisch pneumotachograph and electrical integrator (Sanborn No. 350-3700A) connected in series with the spirometer. The amplitudes of these volume signals differed by less than 3% with frequencies up to 40 cycles per minute.

The instantaneous CO<sub>2</sub> concentration at the mouth was monitored continuously by a rapid infrared analyzer which was calibrated with known gas mixtures of CO<sub>2</sub>. Minute ventilation, the product of tidal volume at the mouth and respiratory frequency, was measured at 10 to 25 points during each sequence of rebreathing and compared with the simultaneous end-expiratory concentration of CO<sub>2</sub>.

Rebreathing was continued until the first of three criteria became evident: (1) three minutes had elapsed, (2) the end-expiratory concentration of CO<sub>2</sub> rose to 9%, or (3) the subject became anxious or uncomfortable. The concentration of oxygen in the balloon remained in excess of 21% after rebreathing for three minutes. In general, the patients with stroke rebreathed CO<sub>2</sub> for a shorter period than normal subjects (mean time 2.4 and 3.0 minutes, respectively).

At the same time that the ventilatory response to CO<sub>2</sub> was measured, the motor output of the respirator center was assessed by measuring the rate of mechanical work (power). The rebreathing circuit consists of a patient mouthpiece (A) and three-way stopcock (B), through which the patient either breathes 35% oxygen or rebreathes from the meteorological balloon (C). Respiratory volume changes are recorded directly with a spirometer (D) connected to the plexiglass box surrounding the balloon. An electrical signal proportional to volume is generated by a precision rotary potentiometer (E), which is attached to the pulley of the spirometer. The viscous airway resistance element, when used, is inserted between (A) and (B).
exerted upon the lungs by the inspiratory muscles of respiration.\textsuperscript{13} Transpulmonary pressure, obtained from a differential strain gauge between the mouthpiece and an esophageal balloon, was plotted against simultaneous changes in respiratory volume on an X-Y recorder (Hewlett-Packard 7004-A). The mechanical inspiratory work performed upon the lungs during each breath was measured by planimetry of the resulting transpulmonary pressure-volume loops, adding the area of the inspiratory half of the pressure-volume loop, representing nonelastic work, to the area of a triangle representing elastic work (fig. 2). Inspiratory power, extrapolated over the time of one minute, is represented by the product of inspiratory work per breath and respiratory frequency. The inspiratory power exerted upon the chest wall and the possible negative work performed by the inspiratory muscles of respiration were not estimated.

The stability of tidal volumes and minute ventilation during resistive loading of the respiratory system was tested by placing two sintered bronze disks within the mouthpiece of the rebreathing apparatus (fig. 1), simulating an added viscous airway resistance of 3.4 cm water per liter per second. The pressure-flow characteristics of this resistance were linear up to a flow rate of 2.5 liters per second. The carbon dioxide rebreathing test was then repeated and the responses of ventilation and inspiratory power to CO\textsubscript{2} were analyzed under otherwise identical conditions. Since airway pressure was measured between the sintered bronze disks and the meteorological balloon, at point B in figure 1, the mechanical inspiratory work performed upon the external airway resistance was measured, as well as the work performed upon the lungs.

The relationship of either minute ventilation or inspiratory power to the simultaneous end-expiratory carbon dioxide tension was analyzed by least squares regressions.\textsuperscript{13} The effect of the external viscous airway resistance upon the response to CO\textsubscript{2} was tested by the “t” test of paired differences in each individual.\textsuperscript{14} Comparisons of the slopes of regressions between patients and normal subjects were made by multiple regression analysis.\textsuperscript{15}

Correlations between the elastic inspiratory work per breath, represented by the hatched triangle in figure 2, and the end-expiratory CO\textsubscript{2} tension was analyzed with least squares regressions for the control subjects and patients, while breathing through an unobstructed external airway. Correlations between the nonelastic inspiratory work per breath, represented by the left half of the hatched ellipsoid in figure 2, and the end-expiratory CO\textsubscript{2} tension were performed under the same conditions.

The dynamic pulmonary compliance (Cl dyn) was determined from transpulmonary pressure-volume loops by measuring the ratio of the change in lung volume to the change in the transpulmonary pressure between the points of end-inspiration and end-expiration (fig. 2). In normal subjects, this estimate agreed closely with measurements of quasi-static compliance made at one liter above the functional residual capacity. No attempt was made to control the volume history of the lungs prior to the measurements of Cl dyn in normal subjects, since the volume history could not be similarly controlled in patients.

Within 24 hours after the CO\textsubscript{2} response studies, arterial blood samples were obtained from the patients, who were kept at bed rest breathing ambient air for this determination. The arterial oxygen and carbon dioxide tensions and pH were measured at $37^\circ$ C using standard electrochemical techniques. Anaerobic temperature corrections were unnecessary since none of the patients was febrile at the time of the study.

Four of the patients with stroke (Case Nos. 2, 5, 7, and 9) were studied in the supine position. No significant differences were noted in dynamic compliance, arterial oxygen tension, and the responses to CO\textsubscript{2} inhalation between these patients and those studied while seated. For this reason, the data for patients studied in either position were pooled.

### Results

Table 3 shows the responses of minute ventilation and inspiratory power to CO\textsubscript{2} inhalation in normal subjects and patients with stroke. In normal subjects with an unobstructed airway, the ventilatory response to CO\textsubscript{2} was $2.53$ liters $\times$ min$^{-1}$ $\times$ (mm Hg Pco$_2$)$^{-1}$ (Lpmm), a value which decreased slightly to $2.12$ Lpmm breathing through a viscous airway resistance (fig. 3A). The patients with cerebral infarction showed a higher ventilatory response ($3.21$ Lpmm) while breathing through an unobstructed airway and a significant decrease ($P < 0.05$) to $2.26$ Lpmm while breathing through an external airway resistance (fig. 3B). The extrapolated carbon dioxide tensions at a minute ventilation value of zero were not significantly different in the two groups.

In normal subjects breathing through an unobstructed external airway, the inspiratory power response to CO\textsubscript{2} was $0.25$ kilogram-meters $\times$ min$^{-1}$ $\times$ (mm Hg Pco$_2$)$^{-1}$ (kgmm). This value
TABLE 3
Comparison of Normal Subjects and Patients With Unilateral Cerebral Arterial Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Cerebral arterial occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response of inspiratory power to CO₂ stimulation, kgmm</strong>^a^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline condition ± SEM</td>
<td>0.25 ± 0.05</td>
<td>0.68 ± 0.14</td>
</tr>
<tr>
<td><strong>Viscous airway resistance ± SEM</strong></td>
<td>0.40 ± 0.07</td>
<td>0.77 ± 0.16</td>
</tr>
<tr>
<td><strong>Minute ventilation response to CO₂ stimulation, Lpmm</strong>^§^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline condition</td>
<td>2.53 ± 0.32</td>
<td>3.21 ± 0.59</td>
</tr>
<tr>
<td><strong>Viscous airway resistance</strong></td>
<td>2.12 ± 0.23</td>
<td>2.26 ± 0.49</td>
</tr>
<tr>
<td><strong>Calculated P_{CO_2} at zero inspiratory power, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline condition</td>
<td>44.8 ± 1.4</td>
<td>41.2 ± 1.8</td>
</tr>
<tr>
<td><strong>Viscous airway resistance</strong></td>
<td>45.2 ± 0.5</td>
<td>39.9 ± 2.7</td>
</tr>
<tr>
<td><strong>Calculated P_{CO_2} at zero ventilation, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline condition</td>
<td>40.6 ± 1.4</td>
<td>34.2 ± 3.2</td>
</tr>
<tr>
<td><strong>Viscous airway resistance</strong></td>
<td>40.0 ± 0.9</td>
<td>28.11 ± 6.10</td>
</tr>
</tbody>
</table>

*Kilogram—meters × min⁻¹ × (mm Hg P_{CO_2})⁻¹.

^P < 0.001.

^§P < 0.01.

^§Liners × min⁻¹ × (mm Hg P_{CO_2})⁻¹.

||P < 0.05.

SEM: standard error of the mean.

increased in 12 of the 13 subjects to a mean level of 0.40 kgmm (P < 0.01) after addition of the viscous resistance (fig. 4A). The inspiratory power response in the patients with stroke breathing through an un-

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3**

A. Normal subjects. B. Patients. The response of minute ventilation to carbon dioxide is shown. The solid lines are the responses while breathing through an unobstructed airway, and the dotted lines are the responses breathing through the viscous airway resistance element.
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...obstructed airway was 0.68 kgmm, and increased only insignificantly to 0.77 kgmm with the added resistance (fig. 4B). Although the inspiratory power response did not increase significantly in these patients when the resistance was added, all measured levels were much higher than those observed in normal subjects (P < 0.001, table 3). There were no significant differences observed between normal subjects and patients in the calculated CO₂ tensions at a zero level of inspiratory work.

The effect of age upon the ventilatory and inspiratory power responses to CO₂ was tested by studying four elderly normal subjects, aged 51 to 75 years (Cases 14, 15, 16, and 17, table 2). Three of these four subjects showed a significant increase in inspiratory power while breathing through the viscous airway resistance — findings similar to those obtained in the young normal group. Significant differences were not observed between the results of these studies in elderly persons and the results in young normal subjects.

An additional five normal subjects breathed CO₂ through an external resistance of 9.8 cm H₂O per liter per second in the baseline condition, to simulate the inspiratory power observed in patients in the baseline condition. When these normal subjects breathed through a higher external resistance (13.4 cm H₂O per liter per second), with an increment equal to the external resistance used in stroke patients, only a slight, insignificant increase was observed in the inspiratory power response to CO₂ (slope = 0.35 ± 0.01 and 0.42 ± 0.01 kgmm, respectively, P = 0.20).

The high inspiratory power response to CO₂ observed in the patients also was investigated by an analysis of the changes in frequency, elastic work per breath, and nonelastic work per breath during the inhalation of carbon dioxide. The response of respiratory frequency to CO₂ in patients was 0.483 breath X minute⁻¹ X (mm Hg Pco₂)⁴ (Bpmm), which was not significantly different from the value of 0.388 Bpmm in the normal group. However, the mean respiratory frequency during the test was higher in the patients (27.7 breaths per minute) than in the normal subjects (16.4 breaths per minute, P < 0.001). The elastic inspiratory work performed during each breath was consistently greater in the patients for any level of inspiratory CO₂ (fig. 5). Nonelastic (resistive) work per breath plotted against the tension of CO₂ revealed a steeper slope (P < 0.001) in patients (fig. 6).

Dynamic compliance of the lungs (Cl dyn) measured during the first one to two breaths of CO₂ inhalation was normal in the control subjects (mean of 0.24 liter per centimeter H₂O) and was lower in...
patients (mean of 0.136 liter per centimeter H$_2$O) (P < 0.001). Measurements of Cl dyn at several respiratory frequencies during CO$_2$ inhalation in normal subjects (fig. 7A) and in patients (fig. 7B) revealed modest decreases at higher respiratory frequencies in five of the 12 patients and in five of the 13 normal subjects. At a mean baseline breathing frequency for normal subjects of 12 breaths per minute, the extrapolated Cl dyn in patients also was low (mean of 0.14 liter per centimeter H$_2$O).

Moderate arterial hypoxemia while breathing ambient air was observed in seven of the 11 patients tested and hypocapnic alkalosis occurred in five (table 1). The calculated value of serum bicarbonate was normal in each determination, however, suggesting that hyperventilation occurred acutely and was caused by the arterial puncture. The tension of oxygen in arterial blood was not significantly related to the Cl dyn measured during the first one to two breaths of CO$_2$ in patients (r = 0.018).

**Comments**

The rebreathing technique employed in the present investigation has been found to permit valid estimations of CO$_2$ tensions in arterial and mixed venous blood and at the medullary chemoreceptors, despite large variations in cerebral blood flow. For these reasons, the techniques were considered suitable for use in studying the interaction of CO$_2$ tension and the regulation of breathing. An initial concentration of 35% oxygen was chosen for the rebreathing test in the expectation that this modest increment would be less likely than would pure oxygen to modify respiration in patients with hypoxemia. Under the conditions of this experiment, the inspiratory concentration of oxygen was at least equal to that in ambient air, and hypoxic stimulation of respiration should not have been greater than that present prior to our testing. In only three patients was hypoxemia of sufficient severity while breathing ambient air to cause a significant stimulation of respiration and that contribution to ventilatory drive should have been obviated by the use of a 35% oxygen mixture during the performance of these studies.

Our findings in the normal subjects were similar to those obtained by others in regard to: values for inspiratory power during the first two inhalations of CO$_2$, increases in minute ventilation and inspiratory...
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A. Normal subjects. B. Patients. The pulmonary dynamic compliance is shown for representative respiratory frequencies observed during the inhalation of CO₂.

power with CO₂ inhalation, and the small decrement in the ventilatory response to CO₂ when breathing through a small external resistance. A larger decrease in the ventilatory response to CO₂ has been observed by others, however, when a much higher mechanical load was added to the external airway.⁸ ¹⁰ ¹¹ During resistance breathing in this study, normal subjects increased the mechanical power applied to the lungs appropriately, in that the ventilatory response to CO₂ remained unchanged. These observations differ from those of other investigators in humans,⁸ but confirm the results obtained in animal models.²² It is likely that a significant increase in mechanical power was observed when our normal subjects breathed through an airway resistance because the techniques employed in this study permitted the accumulation of many more data points, thereby facilitating precise determination of the quantitative relationship between inspiratory power and the carbon dioxide tension.

The present studies show that the respiratory function of patients with unilateral cerebral infarction differs from that of normal subjects in three significant respects: (1) the mechanics of ventilation were abnormal, (2) hypoxemia was present in seven patients, and (3) the inspiratory power during CO₂ breathing was high under baseline condition, while a further, expected increase failed to occur during resistance breathing.

One possible explanation for the abnormalities observed in patients with stroke could be the age difference between this group and our normal subjects. Aging alone, however, should not have caused the low dynamic compliance, since this measurement remains the same or increases in older persons.²³ Moreover, we could not find a significant correlation (r = 0.16) between the age (19 to 56 years) and inspiratory power in the seven normal subjects reported by Fritts¹⁹ or in the older normal subjects in the present report. For these reasons, the effect of age does not appear to explain the differences between our normal subjects and the patients with stroke.

A second possibility is that the abnormalities in respiratory function in our patients were due to an abnormality in the end organ, the lungs and respiratory muscles. Conditions such as atelectasis and airway obstruction would be generally accompanied by arterial hypoxemia as well as reduced compliance. A statistically significant relationship between these measurements could not be demonstrated, however. Clinically inapparent chronic obstructive pulmonary disease could have caused arterial hypoxemia and a high level of nonelastic work in the patients with stroke, but would not explain the high level of elastic work, the decreased compliance, or the inspiratory power responses which were observed in these patients.²⁴ Although a metabolic limitation of the inspiratory forces generated by the muscles of respiration could have prevented a further increase in inspiratory power during resistance breathing, this limitation could not account for the abnormalities observed in ventilatory mechanics. Moreover, a plateau in the increases in inspiratory power during the inhalation of CO₂ did not occur in any patient.

The mechanical abnormalities described in our patients could be explained readily by the presence of pulmonary edema or congestion. High levels of both elastic and nonelastic resistance, as well as hypoxemia and alveolar hyperventilation, are commonly observed in patients with pulmonary edema.²⁵ ²⁶ Although congestion of the pulmonary vascular bed has not been
previously reported in patients with cerebral infarction, pulmonary congestion ranging in severity from interstitial fluid accumulation to alveolar edema has been reported in patients after gross cerebral trauma. In animals with experimentally increased intracranial pressure.

Because of the possibility of subclinical pulmonary congestion in the patients with stroke, the chest x-rays of these patients were reviewed. Evidence of pulmonary congestion and cardiomegaly was observed in the films of Patient No. 6, who had the highest levels of inspiratory power in response to CO₂ (1.8 kgmm) and the highest mean level of inspiratory work of any patient studied during the exposure to CO₂. The erect chest films of Patients No. 5 and 10 showed cardiomegaly and increased vascularity in the upper lung fields. The inspiratory power responses of these latter three patients (1.32 ± 0.26 kgmm), who showed some clear evidence for pulmonary congestion by radiological examination, were found to be significantly greater than the responses in the remaining patients (0.47 ± 0.09 kgmm, P < 0.01). Lesser degrees of pulmonary congestion might easily have been overlooked in the films of the remaining patients. Although the available data cannot be regarded as proving the presence of pulmonary edema in our patients with stroke, the abnormalities observed in ventilatory mechanics and intrapulmonary gas exchange appear to be explained satisfactorily by this hypothesis. It is possible that the mechanisms which cause pulmonary edema after severe cerebral trauma may be operative in lesser degree after any form of damage to the cerebral hemispheres.

The stability of tidal volumes and minute ventilation was evidently poor in the patients, as was demonstrated by the significantly diminished ventilatory response to CO₂ while breathing through a small external resistance to airflow. The normal subjects, in contrast, increased their level of inspiratory work appropriately to the imposed resistive load and thus maintained the same ventilatory responses to CO₂ that prevailed in the baseline, unloaded condition. The patients may have failed to detect the additional resistance because of some defect in proprioceptive feedback from the lungs and chest wall. Our observation that the same deficit in proprioception could be simulated in normal subjects by preloading the respiratory system with a large external resistance, however, makes this possibility unlikely. Since conscious detection of an added resistive load reportedly depends upon the ratio of the added resistance to the baseline pulmonary resistance, it is more likely that the added viscous resistance was too low for detection against a background of the high baseline pulmonary resistance which prevailed in our patients.

The patients reported in the present study were chosen, in part, because of their stable clinical condition and their ability to tolerate the studies easily. Although they were severely ill, all were able to respond meaningfully to the experimental milieu. The combination of high levels of elastic and viscous resistances to ventilation and an elevated threshold for the detection of resistive loading of the respiratory system in some more severely afflicted patients than those reported here may account for the occasional instances of respiratory failure among these individuals.

References

CORRECTION

Due to an error in editing, the figures and legends do not correspond in the article by Meyer et al. The legends should be as follows:
The legend for figure 8, which appears on page 192, is actually the legend for figure 1, which appears on page 183.
The legend for figure 9, which appears on page 193, is actually the legend for figure 2, which appears on page 184.
The legend for figure 1, which appears on page 183, is actually the legend for figure 3, which appears on page 187.
The legend for figure 2, which appears on page 184, is actually the legend for figure 4, which appears on page 188.
The legend for figure 3, which appears on page 187, is actually the legend for figure 5, which appears on page 189.
The legend for figure 4, which appears on page 188, is actually the legend for figure 6, which appears on page 190.
The legend for figure 5, which appears on page 189, is actually the legend for figure 7, which appears on page 191.
The legend for figure 6, which appears on page 190, is actually the legend for figure 8, which appears on page 192.
The legend for figure 7, which appears on page 191, is actually the legend for figure 9, which appears on page 193.
The Mechanics of Breathing and Stabilization of Ventilation in Patients With Unilateral Cerebral Infarction

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