Human Cerebrovascular Response to Combined Hypoxia and Hypercapnia

By William Shapiro, M.D., Albert J. Wasserman, M.D., and John L. Patterson, Jr., M.D.

ABSTRACT

The N₂O technique was used in 6 human subjects to measure cerebral blood flow and metabolism during hypoxia and hypercapnia induced by the inhalation of 10% O₂-5% CO₂. Ventilation increased from 7.7 to 48.3 liters/min; Paco₂ decreased from 88 to 62 mm Hg; Paco₂ increased from 38 to 45 mm Hg (for each P<.01). Mean cerebral blood flow increased from 56 to 97 ml/100 g/min (P< .01). Because cerebral O₂ consumption was unchanged, the technique of estimating changes in cerebral flow from arterial-jugular venous O₂ differences was used to follow changes during the first 10 min of inhalation of 10% O₂-5% CO₂ in 6 additional subjects. The rapidity of cerebral vasodilatation was increased by this combination of stimuli. The enhanced respiratory response produced by breathing 10% O₂-5% CO₂ appeared responsible for the more rapid cerebrovascular response and may offer some protective benefits. Comparisons of the present data with previous studies lead to the conclusion that simultaneous hypoxia and hypercapnia have additive dilator effects on the cerebral vasculature. Thus, the observed increases in cerebral flow were the sum of their individual effects.

ADDITIONAL KEY WORDS

respiratory response cerebral blood flow cerebral metabolism

temporal pattern of response jugular venous blood gas tensions cerebral vasodilatation additive effects

cerebrovascular resistance arterial blood gas tensions unanesthetized man

Hypoxia and hypercapnia, acting separately, increase cerebral blood flow (1-4). Little is known of the simultaneous effects of these stimuli even though they frequently occur together in clinical situations. Although one might predict that their effects are additive in normal man, quantitative data are not available.

Lennox and Gibbs (5) in 1932 showed that inhalation of high CO₂-low O₂ mixtures resulted in slightly narrower arteriovenous O₂ differences (i.e. higher cerebral blood flow) than high CO₂-normal O₂ mixtures. Gas concentrations and sampling times were variable in this pioneering study, and others have concluded that the combined effects of high CO₂-low O₂ were not greater than those of high CO₂ alone (6). Gibbs and colleagues (7) demonstrated that breathing 5% CO₂ counteracted some of the cerebral effects of extreme hypoxemia. They showed that maintaining a higher arterial blood CO₂ tension by having subjects inhale 5% CO₂ during hypoxia sustained consciousness longer and preserved normal electroencephalographic patterns even when subjects breathed as little as 2% O₂.

Patterson and colleagues (8) investigated the cerebral circulation and metabolism in the naturally occurring model provided by patients with chronic pulmonary emphysema with secondary hypoxia and hypercapnia.

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Cerebral blood flow was increased in their patients, and aggravation of hypercapnia by inhalation of pure \( \text{O}_2 \) mixtures was associated with further increases in flow. Their data were thought not to be comparable to those obtained in normal men, because there may have been adaptive responses peculiar to a slowly developing chronic disease.

The purpose of the present study was to measure the cerebrovascular response to simultaneous hypoxia and hypercapnia in normal man. Since under the conditions of this study alterations in the cerebral \( \text{O}_2 \) consumption did not occur, we followed the early phases of the response by measuring the changes in the difference between arterial and jugular venous \( \text{O}_2 \) content (2, 3, 9).

**Methods**

The subjects were normal adult volunteers aged 21 to 37 years (mean, 29). All studies were done in the forenoon with subjects in the supine position.

1. Cerebral blood flow was measured in 6 subjects by the nitrous oxide method of Kety and Schmidt (10) as modified in this laboratory (11). The subjects breathed 15\% \( \text{N}_2 \)O-21\% \( \text{O}_2 \)-64\% \( \text{N}_2 \) for 12 min. Paired blood samples for measurement of \( \text{N}_2 \)O, \( \text{O}_2 \), and \( \text{CO}_2 \) contents and \( \text{pH} \) were withdrawn from indwelling needles placed percutaneously in the brachial artery and in the internal jugular bulb after local anesthesia. After a control resting determination followed by a 20-min rest period, the subjects breathed a gas mixture containing 10\% \( \text{O}_2 \), 5\% \( \text{CO}_2 \), and 85\% \( \text{N}_2 \). At the end of 10 min they were switched without interruption to a mixture containing 10\% \( \text{O}_2 \), 5\% \( \text{CO}_2 \), 15\% \( \text{N}_2 \)O, and 70\% \( \text{N}_2 \). At this point the experimental cerebral blood flow determination was begun and continued for the succeeding 12 min. Minute ventilation was measured by pneumographs on the lower thorax and epigastrium; the pneumographs were calibrated at the time of each experiment by having the subject breathe into a spirometer. Arterial pressure was recorded with a Statham P23Db transducer and an electronic multichannel oscillographic recorder (Electronics for Medicine, Inc., Model DR8, White Plains, New York). Mean pressures were obtained by electronic integration. Continuous recording and monitoring of lead II of the electrocardiogram was also carried out on the same instrument. No abnormalities were seen in the monitored electrocardiogram in any of the experiments.

The \( \text{N}_2 \)O content of the blood was determined by the method of Kety and Schmidt with slight modifications (11). The \( \text{O}_2 \) saturation of arterial and jugular venous blood was determined by a spectrophotometric technique (12). Arterial \( \text{O}_2 \) and \( \text{CO}_2 \) tensions were determined by electrodes (13) using an Esco apparatus (Esco, Inc., Cambridge, Mass.). \( \text{pH} \) was also measured on this apparatus with a Metrohm electrode at 37°C.

The cerebral \( \text{O}_2 \) consumption was calculated as the product of cerebral blood flow and cerebral arterial-jugular venous \( \text{O}_2 \) difference. Cerebrovascular resistance was calculated by dividing the mean arterial pressure by the cerebral blood flow.

2. The series of experiments described demonstrated that cerebral \( \text{O}_2 \) consumption did not change significantly after simultaneous inhalation of 10\% \( \text{O}_2 \)-5\% \( \text{CO}_2 \). It was therefore possible to use the \( 1/(\text{A} - \text{V})\text{O}_2 \) technique (2, 3, 9) in a second series of six studies designed to follow more rapid changes in the pattern of the response. Using this technique, the reproducibility of cerebral blood flow measured in a steady state has been found to be \( 3.4\% \pm 5.2\% \) in this laboratory (3). After obtaining control samples, the subjects were given 10\% \( \text{O}_2 \)-5\% \( \text{CO}_2 \)-85\% \( \text{N}_2 \) to breathe, and paired arterial and jugular venous blood samples were obtained every minute for 10 min. Analyses for \( \text{O}_2 \) content, \( \text{O}_2 \) and \( \text{CO}_2 \) tensions, \( \text{pH} \) and recording of arterial blood pressure and minute ventilation allowed us to calculate all the values, except cerebral \( \text{O}_2 \) consumption obtained by the \( \text{N}_2 \)O technique.

Statistical analyses were carried out by standard methods (14) with the aid of a digital computer.

**Results**

1. As shown in Table 1, cerebral \( \text{O}_2 \) consumption, arterial and jugular venous \( \text{pH} \) and jugular venous \( \text{CO}_2 \) tension were not significantly altered by breathing a mixture of 10\% \( \text{O}_2 \), 5\% \( \text{CO}_2 \), 85\% \( \text{N}_2 \). The cerebrovascular resistance decreased and cerebral blood flow increased. There was no material difference between cerebral blood flow expressed as percent of control estimated from arterial-jugular venous \( \text{O}_2 \) difference and that measured by the \( \text{N}_2 \)O technique. Although arterial \( \text{O}_2 \) tension decreased, jugular venous \( \text{O}_2 \) saturation and tension rose.

To determine whether hypoxia and hypercapnia have additive effects, we compared the data obtained during combined hypoxia and hypercapnia with those obtained during ex-
**Effects of Inhalation of 10% \( \text{O}_2 \)-5% \( \text{CO}_2 \) on Cerebral Blood Flow and Metabolism, Ventilation, Pulse, Mean Blood Pressure and Blood Constituents**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean</th>
<th>Pulse</th>
<th>Mean BP</th>
<th>CBF (ml/100g/min)</th>
<th>CMRO (_2) (ml/O2/min/lOOg tissue)</th>
<th>CVR (mm Hg/ml/100g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.1</td>
<td>52.9</td>
<td>86.3</td>
<td>7.34</td>
<td>7.31</td>
<td>7.33</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>42.7</td>
<td>74.1</td>
<td>7.38</td>
<td>7.36</td>
<td>7.39</td>
</tr>
<tr>
<td>3</td>
<td>5.8</td>
<td>41.7</td>
<td>71.7</td>
<td>7.33</td>
<td>7.36</td>
<td>7.41</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
<td>39.4</td>
<td>62.0</td>
<td>7.34</td>
<td>7.32</td>
<td>7.39</td>
</tr>
<tr>
<td>5</td>
<td>7.3</td>
<td>50.2</td>
<td>63.3</td>
<td>7.37</td>
<td>7.37</td>
<td>7.41</td>
</tr>
<tr>
<td>Mean</td>
<td>7.7</td>
<td>46.3</td>
<td>66.6</td>
<td>7.35</td>
<td>7.35</td>
<td>7.37</td>
</tr>
</tbody>
</table>

**TABLE 1**

*\( P < .01 \).*

*\( P > 0.05 \) (not significant).*

C = control; E = experimental; V = minute ventilation; art. BP = arterial blood pressure; CBF = cerebral blood flow; CMRO \(_2\) = cerebral \( \text{O}_2 \) consumption; CVR = cerebrovascular resistance.
Exposure to hypoxia and hypercapnia separately. Reduction of arterial O₂ tension to the level found in this study (54 to 69, mean 62 mm Hg) has been associated with barely detectable, or no, rise in cerebral blood flow (15, 17) (see line 2, Table 5). In Table 2, therefore, we have compared the mean effects of 5% CO₂ alone with those of 10% O₂ and 5% CO₂ during steady states. Lambertsen et al. (18) found the "cerebral blood flow index" to be 135% of control when arterial CO₂ tension was raised from 44 to 50 mm Hg. This estimate was based on arterial-jugular venous O₂ differences obtained in the steady state and would best be compared to our mean value of 158%. Inhalation of 5% CO₂ was associated with rises in cerebral blood flow from 54 to 86 ml/100 g per min [Kety and Schmidt (1), 6 subjects] and from 53 to 74 ml/100 g per min [Novack et al. (19), 12 subjects]. The increase in cerebral blood flow in Table 1 was greater than one would predict from the known effects of breathing 5% CO₂. An attempt was made to pool data from the present series with comparable data from Kety and Schmidt (1) and Novack et al. (19), in order to state the significance of the differences in results. F values derived when the three groups were pooled in regression were not significant. However, the intragroup variations were as great as the intergroup variations, which suggests that it may not have been valid to attempt to compare these groups statistically. Variations in laboratory techniques and relatively small numbers in each group may well account for this evident incomparability.

2. The temporal pattern and magnitude of the mean changes during the first 10 min of breathing 10% O₂-5% CO₂ are shown in Table 3. Data from an individual study are shown in Figure 1. Significant changes in cerebral blood flow and arterial O₂ and CO₂ tensions occurred at the end of 1 min. By the end of the second minute, mean cerebral blood flow was within 3% of its 10-min value. Mean arterial O₂ tension was within 1 mm Hg of its final value and mean arterial CO₂ tension was 2 mm Hg less than its final value at the end of the second and first minutes, respectively. In contrast, minute ventilation required 4 min to become stable, and a slight upward trend was seen at 9 and 10 min. Jugular venous CO₂ and O₂ tensions did not change significantly, nor did mean arterial pressure or venous pH, except at the end of 1 min.

Table 4 compares this study with similar

![Pattern of change in cerebral blood flow (CBF), arterial and jugular venous gas tensions in 1 of 6 subjects during the first 10 min of inhalation of 10% O₂-5% CO₂-85% N₂.](#)

### Table 2

<table>
<thead>
<tr>
<th>Series</th>
<th>Mixture inhaled</th>
<th>PaCO₂</th>
<th>C</th>
<th>E</th>
<th>CBF</th>
<th>1/(A–V)O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mm/Hg</td>
<td></td>
<td>mll/100g/min</td>
<td>% control</td>
</tr>
<tr>
<td>Present</td>
<td>10% O₂-5% CO₂</td>
<td>36</td>
<td>44</td>
<td></td>
<td>56</td>
<td>74</td>
</tr>
<tr>
<td>Ref. 1</td>
<td>5% CO₂</td>
<td>43</td>
<td>50</td>
<td></td>
<td>54</td>
<td>89</td>
</tr>
<tr>
<td>Ref. 17</td>
<td>5% CO₂</td>
<td>44</td>
<td>50</td>
<td></td>
<td>53</td>
<td>74</td>
</tr>
<tr>
<td>Ref. 19</td>
<td>5% CO₂</td>
<td>43</td>
<td>50</td>
<td></td>
<td>53</td>
<td>74</td>
</tr>
</tbody>
</table>

C = control; E = experimental; PaCO₂ = arterial blood carbon dioxide tension.
studies of the effects of each gas given alone previously reported from this laboratory (3, 4, 15). These data indicate that the separate effects of comparable degrees of hypoxia and hypercapnia may account for the present results. During inhalation of 10% O₂ for 8 min, peak cerebral blood flow occurred in an average of 6.6 min, and the magnitude of increase in flow appeared to depend on the level of the associated hypocapnia. The mean arterial O₂ tension after inhalation of 10% O₂ for 10 min was about 40 mm Hg. At a mean arterial O₂ tension of 53 mm Hg, comparable to that in the present series, mean cerebral blood flow was 1082% of control. During administration of 5% CO₂ alone, arterial CO₂ tension rose to within 3 mm Hg of its final value in 126 ± 77 sec, and cerebral blood flow rose to within 12% of its final value in an average of 156 ± 77 sec after onset of the CO₂ inhalation. Cerebral blood flow was increased to 117% and 141% above control when arterial CO₂ tension was 5 and 10 mm Hg above control, respectively. Table 5 compares the values for cerebral blood flow determined 1 min after beginning inhalation of 10% O₂-5% CO₂, 10% O₂ alone, and 5% CO₂ alone. The combination of 10% O₂ and 5% CO₂ in the present series caused a more rapid response than either agent alone, but the ultimate rise in cerebral blood flow appears to be due to the additive effects of the induced alterations in the blood gases.

**TABLE 3**

Alterations in Mean Values for Cerebral Blood Flow, Ventilation, Blood Constituents and Mean Arterial Pressure in 6 Subjects during Each of the First 10 Min of Inhalation of 10% O₂ + 5% CO₂

<table>
<thead>
<tr>
<th>Time</th>
<th>CBF</th>
<th>Pco₂</th>
<th>A-Pco₂</th>
<th>PaO₂</th>
<th>Paco₂</th>
<th>pH</th>
<th>MABP</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>mm Hg</td>
<td>% control</td>
<td>mm Hg</td>
<td>A</td>
<td>V</td>
<td>A</td>
<td>V</td>
</tr>
<tr>
<td>Control</td>
<td>100</td>
<td>36</td>
<td>46</td>
<td>87</td>
<td>25</td>
<td>7.43</td>
<td>7.37</td>
</tr>
<tr>
<td>1</td>
<td>124+</td>
<td>41+</td>
<td>47</td>
<td>55+</td>
<td>26</td>
<td>7.40+</td>
<td>7.36+</td>
</tr>
<tr>
<td>2</td>
<td>132+</td>
<td>41+</td>
<td>47</td>
<td>53+</td>
<td>27+</td>
<td>7.39+</td>
<td>7.36</td>
</tr>
<tr>
<td>3</td>
<td>134+</td>
<td>40+</td>
<td>48</td>
<td>53+</td>
<td>27</td>
<td>7.39+</td>
<td>7.36</td>
</tr>
<tr>
<td>4</td>
<td>133*</td>
<td>41*</td>
<td>48</td>
<td>53+</td>
<td>20</td>
<td>7.40*</td>
<td>7.36</td>
</tr>
<tr>
<td>5</td>
<td>131*</td>
<td>42*</td>
<td>47</td>
<td>53+</td>
<td>26</td>
<td>7.40*</td>
<td>7.36</td>
</tr>
<tr>
<td>6</td>
<td>134*</td>
<td>43*</td>
<td>48</td>
<td>52+</td>
<td>26</td>
<td>7.39+</td>
<td>7.36</td>
</tr>
<tr>
<td>7</td>
<td>131*</td>
<td>43*</td>
<td>48</td>
<td>52+</td>
<td>26</td>
<td>7.39+</td>
<td>7.36</td>
</tr>
<tr>
<td>8</td>
<td>135+</td>
<td>43+</td>
<td>48</td>
<td>52+</td>
<td>26</td>
<td>7.40+</td>
<td>7.36</td>
</tr>
<tr>
<td>9</td>
<td>138+</td>
<td>43+</td>
<td>48</td>
<td>52+</td>
<td>27</td>
<td>7.38+</td>
<td>7.36</td>
</tr>
</tbody>
</table>

CBF = cerebral blood flow; Pco₂ = CO₂ tension; A = arterial blood; V = jugular venous blood; V = minute ventilation; MABP = mean arterial blood pressure.

† = P < .05.
+ = P < .01.

**TABLE 4**

Comparison of Initial Effects of Inhalation of Various Gases at Comparable Degrees of Alteration of Arterial O₂ and CO₂ Tensions on Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of subjects</th>
<th>Gas inspired</th>
<th>Mean PaO₂</th>
<th>Mean ΔPaCO₂</th>
<th>1/(A—V)O₂</th>
<th>CBF</th>
<th>Mean time to peak CBF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present 6</td>
<td>6</td>
<td>10% O₂-5% CO₂</td>
<td>53</td>
<td>+6</td>
<td>134</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Present 18</td>
<td>18</td>
<td>5-7% CO₂</td>
<td>53</td>
<td>+2</td>
<td>108</td>
<td>306</td>
<td></td>
</tr>
</tbody>
</table>

ΔPaO₂ = arterial blood oxygen tension; ΔPaCO₂ = arterial blood CO₂ tension; *Arterial gas tensions were not similar at the time peak flows were reached under each condition.
TABLE 5

Comparison of Blood Gases and Cerebral Blood Flow 1 Min after Beginning Inhalation of Various Gases

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. subjects</th>
<th>Gas inspired</th>
<th>Mean $P_{aO_2}$</th>
<th>Mean $\Delta P_{aCO_2}$</th>
<th>CBF $1/(A-V)O_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>6</td>
<td>10% $O_2$-5% $CO_2$</td>
<td>55 ± 4.0</td>
<td>+5</td>
<td>124 ± 13.5</td>
</tr>
<tr>
<td>4, 15</td>
<td>12</td>
<td>10% $O_2$</td>
<td>62 ± 7.9*</td>
<td>—</td>
<td>98 ± 7.3†</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5-7% $CO_2$</td>
<td>normal</td>
<td>+5-7</td>
<td>118 ± 10.4‡</td>
</tr>
</tbody>
</table>

$P_{aO_2} =$ arterial blood $O_2$ tension; $P_{aCO_2} =$ arterial blood tension.

*Compared to present series, $P < .05$.
†Compared to present series, $P < .01$.
‡Compared to present series, no significant difference.

Discussion

Inhalation of 10% $O_2$-5% $CO_2$ results in alterations in arterial $CO_2$ tension known to be associated with cerebral vasodilatation (1, 2) and depression of arterial $O_2$ tension to levels known to be associated with slight cerebral vasodilatation (15-17). The resultant increases in cerebral blood flow as measured in the steady state by the nitrous oxide method and in the first 10 min of inhalation based on estimates of change in arterial-jugular venous $O_2$ differences appeared to be due to the additive effects of the changes in blood $O_2$ and $CO_2$ tensions. The levels achieved by the $O_2$ and $CO_2$ tensions and their rapid rise were regulated by the known enhanced ventilatory response to $CO_2$ in the presence of hypoxia (17, 20). Although arterial $CO_2$ tension was raised 6 to 7 mm Hg (figures commonly associated with 5% $CO_2$ inhalation, Table 2), on the average, this rise was within the accepted normal range for this gas (35 to 45 mm Hg). The arterial $O_2$ tension, however, fell less than usually observed during inhalation of 10% $O_2$ alone, presumably because of the induced hyperventilation. The associated rises in jugular venous (and probably tissue) $O_2$ tension did not prevent the observed vasodilatation. This has also been observed at similar levels of hypoxia during the inhalation of $CO_2$ in $O_2$ at 147 mm Hg ambient pressure by Pierce et al. (21).

Comparisons of individual and mean data between investigations containing small groups of subjects can lead to inaccurate conclusions because of the considerable spread of the normal cerebrovascular response to changes in blood $CO_2$ tension (3), and because of technical considerations. A less than expected increase in cerebral blood flow such as noted in subject 1 (Table 1), whose arterial $CO_2$ tension rose 11 mm Hg, might well be, for that individual subject, an enhanced response. Repeated studies testing each subject's responsiveness to each stimulus would be necessary for accurate appraisal, and obviously is often impossible. Reivich's calculations (16) of maximum change in cerebral blood flow in response to change in arterial $CO_2$ tension revealed considerable variation between several reported studies that used similar techniques of measurement. Thus, the failure of our attempt to obtain a statistically significant expression of the differences between our results and those of others obtained with 5% $CO_2$ inhalation alone was not surprising. Perhaps more weight should be given to the analyses in Tables 4 and 5, since the data come from the same laboratory. They indicate that while the respiratory response to the combination of gases results in more rapid changes, the ultimate level of cerebral blood flow appears predictable on the basis of the separate effects of hypoxia and hypercapnia. Mild degrees of hypoxia have been thought to be without effect (17), but recent carefully controlled studies show that even minimal hypoxia produces cerebral vasodilatation if the arterial $CO_2$ tension is maintained at the normal level (22).

The question of additive versus synergistic effects of hypoxia and hypercapnia was not settled by the studies of Lennox and Gibbs (5). Their data on cerebral blood flow during
hypoxia were affected by concomitant hypocapnia secondary to the associated hyperventilation. In fact, their mean arteriovenous O₂ difference during inhalation of high CO₂-low O₂ mixtures was slightly narrower than that measured during high CO₂-normal O₂ alone. This would be consistent with the thesis that the effects of "pure" hypercapnia and "pure" hypoxia are additive in normal man. Gibbs and colleagues (7) demonstrated that inhalation of 5% CO₂ counteracted the deleterious effects of severe hypoxemia on cerebral function. Arterial O₂ tension and cerebral blood flow were both increased by this maneuver. The studies of Patterson and colleagues (8) in emphysematous patients with hypercapnia and hypoxia, some of whom also had cor pulmonale, revealed increases in cerebral blood flow "considerably smaller than would be predicted on the basis of the effects produced by rapid alterations in the arterial gas tensions." They suggested that the expected effects of hypercapnia and hypoxia were modified by intrinsic adaptive changes by the cerebral vessels to a chronic disease as well as the heart failure present in some of their subjects. Thus, the present quantitative data are all that are available for this set of conditions in normal man.

The respiratory response to 10% O₂-5% CO₂ with its controlling effect on rate of rise and ultimate level of blood O₂ and CO₂ tensions was undoubtedly responsible for the speed with which the cerebral circulatory changes occurred. Plum and Brown (20) have shown a 79% increase in the ventilatory response to CO₂ in normal subjects when the arterial O₂ tension was 50 mm Hg. Rapid presentation of dilator stimuli to the sensitive control areas therefore occurred under these conditions, but did not significantly alter the magnitude of the cerebrovascular response. In the sense that more rapid vasodilatation may at times be protective to the cerebral tissues, the combination of stimuli is synergistic principally through their effects on the respiratory control mechanism.

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References
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