Depression of Hypoxic Ventilatory Response by Nitrous Oxide

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Ventilatory responses to CO₂ and hypoxia were measured in four normal volunteers breathing 30–50 per cent N₂O with and without added inspiratory resistance. CO₂ response was measured by a steady-state technique, hypoxic response by a non-steady-state progressive technique. Added inspiratory resistance depressed ventilatory responses to both CO₂ and hypoxia. N₂O had no effect on CO₂ response either with or without resistance. N₂O depressed the ventilatory response to hypoxia without added resistance and further depressed the response measured with added resistance. It is thought that this was probably the result of selective depression of peripheral chemoreceptor function by N₂O. (Key words: Ventilation, nitrous oxide; Anesthetics, gases, nitrous oxide; Hypoxia, ventilatory response; Carbon dioxide; ventilatory response.)

The effects of anesthetic gases on the ventilatory response to CO₂ have been well studied.¹–³ However, few data bearing on the effects of these agents on ventilatory response to hypoxia are available. Though N₂O is known not to depress CO₂-driven ventilation, its effect on hypoxic ventilation is apparently unknown. Hypoxic ventilatory response might be important during N₂O anesthesia since N₂O is not always administered with high O₂ concentrations and since hypoxemia may occur with cessation of N₂O administration.

Accordingly, we measured the effects of 35–50 per cent N₂O on ventilatory responses to both hypoxia and hypcapnia. Because of a report⁴ that anesthesia abolished respiratory load-compensating responses, we studied the effect of N₂O on ventilatory response when the respiratory system was loaded with increased inspiratory resistance.

Material and Method

Four male volunteers aged 30–40 years were studied. All were laboratory personnel and had previously undergone measurements of ventilatory control. They breathed through a pneumotachograph (Fleisch No. 3) connected to a low-resistance (Otis–McKerrow) nonrebreathing valve. Flow measured by the pneumotachograph and its integral were recorded on an oscillograph. Gas from the expiratory side of the valve was sampled by rapid-response O₂ (Beckman OM11) and CO₂ (Beckman LB2) meters allowing measurement of end-tidal O₂ (Pₐ₀₂) and CO₂ (Pₐ₉₀₂) tensions. The output of these meters was both recorded on the oscillograph and displayed in digital form. When the effects of added resistance were studied, a standard resistance (14.5 cm H₂O l/sec, linear to 2 l/sec) was added to the inspiratory side of the breathing valve.

The ventilatory response to CO₂ was measured by a steady-state technique. Subjects inspired from a bag containing fixed concentrations of CO₂, N₂O and O₂ in N₂. At least three different CO₂ concentrations were used, with constant N₂O concentrations. Inspired O₂ was such that Pₐ₀₂ was maintained constant at about 115 torr. Subjects breathed each mixture for 8 minutes, after which ventilation, Pₐ₀₂ and Pₐ₉₀₂ were recorded for one minute.

The ventilatory response to hypoxia was assessed by the progressive hypoxia technique of Weil et al.⁵ Subjects breathed from a bag that initially contained 21 per cent O₂ and N₂O in N₂. N₂ and N₂O were added to the bag so that Pₐ₀₂ decreased. CO₂ was added

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Fig. 1. Complete ventilatory responses in one subject. Left panels are CO₂ responses, right panels are hypoxic responses. Abscissee: PAr, (left) and PAO, (right). Ordinates: ventilation; the right scale is twice as expanded as the left. Upper panels are data gathered without added inspiratory resistance, lower panels are data gathered with inspiratory resistance. Circles (○), triangles (△) represent data gathered when the subject was not breathing N₂O. Triangles (△, ▲) represent data gathered when the subject was breathing N₂O. Closed symbols (●, ▲) data gathered without added inspiratory resistance, open symbols (□, ▲) are data gathered with inspiratory resistance.

Results

The N₂O concentrations used produced levels of narcosis such that the subjects did not pay attention to their surroundings and were unable to recall what music they had heard. However, they could be roused and would obey simple commands.

Figure 1 shows data gathered in one subject. The ventilatory response to CO₂ was depressed by added inspiratory resistance but not by N₂O. Depression of the hypoxic response by resistance was not as clear-cut as that of CO₂ response. N₂O significantly depressed hypoxic ventilatory response with or without the resistance.

To examine the effects of resistance or N₂O in the group as a whole, we analyzed response curves such as those shown in figure 1 by comparing ventilation measured...
Fig. 2. Effects of resistance on hypercapnic (left panel) and hypoxic (right panel) ventilation. Ordinates: ventilation with added inspiratory resistance. Abscissae: ventilation without added inspiratory resistance. Open symbols represent control data, closed symbols represent data gathered during \( N_2O \) breathing. On the left, each point compares ventilation measured with and without resistance at the same \( P_{A\text{CO}_2} \) (±2 torr). On the right, each point represents ventilation measured at the same \( P_{A\text{CO}_2} \) (±2 torr). Individual subjects are represented by similar numbers of points.

with and without these influences at the same \( P_{A\text{CO}_2} \) (±2 torr) in hypoxia and at the same \( P_{A\text{CO}_2} \) (±1 torr) in hypercapnia. Similar numbers of such comparisons were made for all individuals and the results were pooled and plotted, as shown in figures 2 and 3.

Figure 2 thus shows, at the same stimulus levels, ventilation with the resistance plotted against ventilation without resistance. For both hypercapnia and hypoxia ventilation tended to be less with resistance than without; the data grouped to the right of the line of identity. This tendency was significant for both hypercapnia and hypoxia \((P < 0.001)\) by t test for paired data). The effects of resistance were similar (analysis of covariance) in hypercapnia and hypoxia and were also similar with and without \( N_2O \) breathing.

Figure 3 indicates the effect of \( N_2O \) on ventilatory control. Ventilation measured during \( N_2O \) breathing is compared with ventilation measured at the same stimulus levels in the absence of \( N_2O \). In the case of hypercapnia, ventilation was not significantly altered by breathing \( N_2O \); data group around the line of identity. With hypoxia, however, ventilation was depressed by \( N_2O \) \((P < 0.001)\) by t test for paired data); the data fall to the right of the line of identity. The effect of \( N_2O \) was significantly \((P < 0.001)\) by analysis of covariance) greater on the hypoxic response than on the hypercapnic response. The pres-
TABLE 1. Hypoxic Response—Values for A

<table>
<thead>
<tr>
<th>Subject</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>137</td>
<td>42</td>
</tr>
<tr>
<td>Resistance</td>
<td>122</td>
<td>56</td>
</tr>
<tr>
<td>Subject 2</td>
<td>228</td>
<td>159</td>
</tr>
<tr>
<td>Control</td>
<td>181</td>
<td>171</td>
</tr>
<tr>
<td>Resistance</td>
<td>218</td>
<td>28</td>
</tr>
<tr>
<td>Subject 3</td>
<td>115</td>
<td>65</td>
</tr>
<tr>
<td>Control</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Resistance</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ence or absence of added inspiratory resistance did not influence the effect of N₂O. When CO₂ was the stimulus, N₂O did not depress ventilation either in the presence of the resistance or in its absence (fig. 3). When hypoxia was the stimulus, N₂O depressed ventilation both in the presence and in the absence of resistance (fig. 3). Both N₂O and the resistance depressed hypoxic response; when both were present hypoxic response was profoundly depressed. At P₁ = 40 torr, only one subject attained a ventilatory rate of 20 l/min breathing N₂O with resistance.

Alternate forms of data analysis were examined. Because our CO₂ response curves were not linear (fig. 1), measurement of their slopes was not thought to be useful. Hypoxic response has been quantitated by Weil et al., in terms of A, a parameter that is related to the increase in ventilation with hypoxia, assuming the V₁–P₁, plot to be a hyperbola. We analyzed our hypoxic responses in this way, and the results are shown in table 1. In all subjects N₂O breathing was associated with a decrease in A. It should be noted that Subject 4 was very unresponsive to hypoxia, demonstrating low values for A during control measurements; when this subject breathed through a resistance A was reduced to zero, indicating that hypoxia was not associated with an increase in ventilation.

Discussion

The clinical state produced by 30–50% N₂O is that described as “dissociation analgesia”; our subjects were unattentive, slightly amnesic, dreaming but rousable. This did not change during the course of the experiment. Cerebral N₂O concentrations are essentially constant after 10 minutes of N₂O breathing, and since our experiments were preceded by at least 10 minutes of N₂O breathing it was probable that the narcosis due to N₂O remained constant throughout. The impairment of consciousness induced by the N₂O made it impossible to deceive the subjects in regard to which experiments involved the anesthetic agent. It also probably minimized the ability of any subject to “cooperate” by consciously altering his breathing pattern. Minute ventilations measured during breathing of air were relatively high and were similar to those recorded during N₂O breathing in the absence of hypoxia or hypercapnia: no excitatory effect on ventilation was found.

We found that N₂O had no consistent effect on ventilatory response to CO₂. This result was not greatly different from that of Eckenhoff and Helrich, who found in one subject that 30 per cent N₂O had a very slight stimulatory effect on CO₂ response. Few analgesies have been studied in terms of both hypoxia and hypercapnic response. Morphine is known to depress both responses. Ventilatory responses to hypercapnia and hypoxia were studied during halothane anesthesia in the dog by Weiskopf et al. They found halothane depressed both responses. We subjected their data to the kind of analysis shown in figure 3, and it appeared that halothane depressed hypoxic responses more than hypercapnic responses. Our result could be explained if N₂O depressed the function of either the peripheral chemoreceptors or their afferent nerves. Other volatile anesthetics may have this property. Halothane depressed the multiplicative interaction of hypoxia and CO₂, which is thought to occur in peripheral chemoreceptors. Dripps and Dumke found that cyclopropane specifically decreased chemoreceptor discharge in response to cyanide injections, suggesting that this agent might specifically reduce hypoxic ventilatory response. However, other investigators subsequently found that cyclopropane per se had no effect on the rate of discharge of carotid chemoreceptors in the unstimulated state. In com-
mon with other gaseous anesthetics. N₂O has been shown to increase discharge from vagal pulmonary stretch receptors in anesthetized animals, but it is not clear how such increased discharge would affect the ventilatory response to either CO₂ or hypoxia. Neither Eckenhoff and Helrich, nor we found consistent tachypnea in studies of man.

Blunted hypoxic response may play a role in the "diffusion hypoxia" observed when N₂O anesthesia is discontinued in the absence of an O₂-enriched mixture. Under these circumstances, the total inert gas concentration in the lung increases rapidly due to N₂O excretion, and PAO₂ is reduced. The only defense available to the patient is hyperventilation in response to hypoxemia. The present results indicate that this defense may be compromised by the anesthetic agent itself.

Added inspiratory resistance has been shown to depress ventilatory responses to both hypercapnia and hypoxia. There is evidence that this effect is more pronounced in hypercapnia than hypoxia, but in the present series the resistance had similar effects on hypoxic and hypercapnic ventilation. This was perhaps because of the relatively small hypoxic ventilatory response we observed. At the levels of ventilation attained in response to hypoxia, both hypoxic and hypercapnic ventilations were only slightly depressed by the resistance, and if responses could have been compared at greater levels of ventilation, differences in the effects of the resistance might have been observed.

We studied the effects of increased resistance because of a report that in goats thiopental anesthesia abolished load-compensating reflexes: inspiratory motor output increased with increased resistance in the awake goat but not when the same animals were anesthetized. We have found (unpublished observations) that meperidine may have a similar effect in man. In the present study, N₂O did not depress the ventilatory response to CO₂ observed with added resistance. This probably indicated that N₂O did not compromise any load-compensating respiratory reflexes that were important in maintaining ventilation in this circumstance.

References