The Effect of Nitrous Oxide on Alveolar Carbon Dioxide Tension:

A Second-gas Effect

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A second-gas effect of nitrous oxide upon alveolar carbon dioxide tension \( (P_{ACO_2}) \) has been demonstrated in decerebrated cats ventilated with a volume-limited respirator. The increase in alveolar tension of carbon dioxide (the second gas) which is associated with the start of administration of nitrous oxide (the first gas) is the result of a concentrating effect produced by rapid absorption of nitrous oxide. At an equilibrated \( P_{ACO_2} \) of 40 torr, administration of 80 per cent nitrous oxide resulted in an increase of \( P_{ACO_2} \) of 2.63 ± 0.29 torr (\( \bar{x} \pm \text{SE} \)). The higher the concentration of nitrous oxide and the lower the level of ventilation (the higher the equilibrated \( P_{ACO_2} \)), the greater the increase in \( P_{ACO_2} \). (Key words: Second-gas effect; Carbon dioxide; Nitrous oxide.)

The rate of uptake of an inert gas depends on a number of factors, including ventilation, blood flow, solubility, and partition coefficient. On the basis of Haggard's early work on uptake of ether,\(^2\) it was assumed for a number of years that the concentration of gas in the inspired air did not affect its relative rate of uptake. However, Eger\(^5\) demonstrated that the higher the concentration of an inert gas in the inspired mixture, the more rapidly it became equilibrated with alveolar gas. Epstein\ et\ al.\( ^4 \) introduced the concept of the second-gas effect, based upon the observation that when a constant concentration of halothane (the second gas) was inspired, the increase in the alveolar concentration of halothane was accelerated by concomitant administration of nitrous oxide (the first gas). They attributed this phenomenon to an increased inspiratory inflow rate produced by the absorption of nitrous oxide from the lung, an increase in inspiratory inflow which was large enough to increase the alveolar halothane concentration. The second-gas effect was first demonstrated during induction of anesthesia with halothane, but it was also later observed with other anesthetic agents after total-body equilibration. Stoelting and Eger\(^5\) demonstrated that the alveolar concentration of ethylene, cyclopropane, or halothane after total-body equilibration could be increased when nitrous oxide was inhaled. Stoelting and Eger have concluded that under different experimental conditions, namely, after total-body equilibration, the second-gas effect is due to an increased concentration of one gas (the second gas) already in equilibration as a result of rapid absorption of another gas (the first gas), rather than the result of an increased volume of inspired gas.

The principles responsible for the second-gas effect are also operative in the decrease in arterial oxygen saturation observed in a subject spontaneously breathing room air during recovery from nitrous oxide–oxygen anesthesia (“diffusion hypoxia”).\(^5,6,8\) The decrease in arterial oxygen saturation during diffusion anoxia is associated with reductions in both end-tidal oxygen (\( P_{O_2} \)) and carbon dioxide (\( P_{ACO_2} \)) tensions.\(^6,10\) Rackow\ et\ al.\( ^9\) postulated that the reverse of these phenomena should occur during the uptake of nitrous oxide, and an increase in \( P_{ACO_2} \) during induction of nitrous oxide anesthesia was, in fact, shown by Heller and Watson\( ^11\) in two subjects, although represented in each by a single

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Fig. 1. Typical polygraph tracing of nitrous oxide and carbon dioxide values in endotracheal gas. Note a rapid increase in end-expiratory Pco2 following the induction of nitrous oxide and a rapid decrease in end-expiratory Pco2 after cessation of nitrous oxide administration. The time scale is 5 seconds.

determination. An increase in Pco2 during induction of nitrous oxide anesthesia, however, has not been demonstrated.

The present investigation was designed to study the effects of administration of various concentrations of nitrous oxide on PA CO2 at times when ventilation was maintained at different steady states.

Method

Ten cats, weighing 3–5 kg each, were anesthetized with nitrous oxide and halothane, following which tracheostomies were performed. A Portex endotracheal tube was inserted through the tracheostomy, an airtight system being assured by silk ligatures tied around the trachea. The right femoral artery and vein were cannulated for pressure monitoring and intravenous infusions, respectively. To permit studies in paralyzed animals without the use of anesthetics, unconsciousness was produced by a combination of electrolytic decerebration (stereotaxic application of 50 milliamperes to the mesencephalic reticular formation for 10 seconds) and ischemic decerebration (bilateral carotid artery ligation). Following decerebration, animals were ventilated with room air and immobilized by continuous intravenous administration of gallamine triethiodide (7–10 mg/kg/hour). Two Beckman-Spinco LB-1 infrared analyzers (one for CO2 and one for N2O) were connected to a 16-gauge sampling needle which extended two inches into the endotracheal tube to allow simultaneous measurements of CO2 and N2O. Care was taken to insure consistency in sizes of needles and tubing, lengths of sampling apparatus, and amounts of sampling air during both calibration and sampling, since changing the total pressure in the sample cell introduced variations of CO2 values. To assure sampling of alveolar gas, a fast speed of polygraph recording was used to record the normal "plateau" of the constant level of end-expiratory Pco2 (PA CO2). To facilitate demonstration of the second-gas effect, the recording speed was slowed (fig. 1). Concentrations of nitrous oxide, carbon dioxide tension, and blood pressure were continuously monitored and recorded on a Grass polygraph. Rectal temperature was maintained at 37 ± 1°C.

Similarity of the spectroscopic absorption spectra of nitrous oxide and carbon dioxide results in a crossover effect between these two gases as measured by the infrared analyzer. To prevent this crossover effect, carbon dioxide and nitrous oxide sampling heads were flooded with 100 per cent nitrous oxide and carbon dioxide, respectively ("head flooding").

In addition to the crossover effect, "pressure or collision broadening effects" were accounted for by using correction factors as described by Severinghaus. Since the diffusion effect of water vapor is counterbalanced by the pressure broadening effect, all CO2 readings were considered dry-gas readings.

Intermittent positive-pressure respiration by means of a nonrebreathing valve and a Harvard volume-limited ventilator was initially maintained with room air for at least two hours. Tidal volume and respiratory rate were adjusted to achieve PA CO2 40 torr. After stable levels of PA CO2 had been maintained for 20 to 30 minutes, nitrous oxide (40 per cent) in oxygen was introduced for 5 minutes, following which room air was again given. Adequate time (1 hour) was then allowed for complete elimination of nitrous oxide and stabilization of PA CO2 prior to the next administration of nitrous oxide. The procedure was repeated with 60 and 80 per cent nitrous oxide.
oxide. Each of the three levels of nitrous oxide was then studied at different starting levels of $P_{ACO_2}$, namely 20, 30, 50, and 60 torr.

Results

The increase in $P_{ACO_2}$ reached its maximum value within a minute of starting nitrous oxide administration and then gradually declined, but still remained above control (pre-nitrous oxide) values for the 5 minutes of nitrous oxide administration. When nitrous oxide was replaced by room air, $P_{ACO_2}$ decreased abruptly and reached control levels in a few minutes. Figure 1 shows a typical abrupt and significant increase of $P_{ACO_2}$ upon the introduction of 60 per cent nitrous oxide at a time when ventilation was stable at $P_{ACO_2}$ of 60 torr.

At equilibrated $P_{ACO_2}$'s of 40 torr and above, all concentrations of nitrous oxide tested (40, 60 and 80 per cent) increased $P_{ACO_2}$. At an equilibrated $P_{ACO_2}$ of 30 torr, both 60 and 80 per cent nitrous oxide increased $P_{ACO_2}$; however, 40 per cent nitrous oxide had no effect. At an equilibrated $P_{ACO_2}$ of 20 torr, no increase of $P_{ACO_2}$ was detected with any concentration of nitrous oxide administered. Figure 2 and table 1 summarize the increases of $P_{ACO_2}$ following the introduction of nitrous oxide after equilibration with room air at various levels of ventilation as measured by end-expiratory $P_{CO_2}$ in equilibration. Ordinate: maximum increase in end-expiratory $P_{CO_2}$ following nitrous oxide administration.

Fig. 2. Abcissa: degree of stabilized ventilation, as indicated by end-expiratory $P_{CO_2}$ in equilibration. Ordinate: maximum increase in end-expiratory $P_{CO_2}$ following nitrous oxide administration.

### Table 1. Maximum increases ($\bar{x} \pm SE$ torr) in end-expiratory $P_{CO_2}$ following administration of nitrous oxide

<table>
<thead>
<tr>
<th>Levels of Stabilized Ventilation (Pstn)</th>
<th>20 torr</th>
<th>25 torr</th>
<th>30 torr</th>
<th>40 torr</th>
<th>50 torr</th>
<th>60 torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 per cent nitrous oxide</td>
<td>0</td>
<td>0</td>
<td>1.36 ± 0.13</td>
<td>2.63 ± 0.29</td>
<td>3.55 ± 0.37</td>
<td>4.96 ± 0.53</td>
</tr>
<tr>
<td>60 per cent nitrous oxide</td>
<td>0.70 ± 0.10</td>
<td>1.50 ± 0.17</td>
<td>1.91 ± 0.22</td>
<td>3.60 ± 0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 per cent nitrous oxide</td>
<td>0</td>
<td>0.07 ± 0.14</td>
<td>1.16 ± 0.12</td>
<td>1.90 ± 0.20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The control end-expiratory $P_{CO_2}$ indicates the degree of stabilized ventilation.
brated $P_{\text{ACO}_2}$, the greater the increase of $P_{\text{ACO}_2}$.

Discussion

One explanation of the second-gas effect is based upon augmented endotracheal flow (Epstein et al.4). Results of the present study cannot be explained by an augmented flow of inspired gas; this would have counteracted any increase in alveolar CO$_2$, because the inspired gas had no significant amount of CO$_2$.

A second explanation of the second-gas effect includes the concentrating effect described by Stoepling and Eger.5 Since in the present studies $P_{\text{ACO}_2}$ was at equilibrium prior to the introduction of nitrous oxide, the increase in $P_{\text{ACO}_2}$ at the start of the administration of nitrous oxide is best explained by this mechanism.

A third possible explanation of the results of the present study may be that an increase in physiologic deadspace ($V_{\text{DP}}$) occurred at the onset of nitrous oxide administration.6 The design of our experiment did not permit evaluation of changes in $V_{\text{DP}}$ produced by nitrous oxide; however, since the increase of $V_{\text{DP}}$ following nitrous oxide administration demonstrated by Askrog et al.6 was related linearly to the duration of anesthesia, it is unlikely that an increase in $V_{\text{DP}}$ plays a major role in the abrupt increase of $P_{\text{ACO}_2}$ observed in this study.

Since vital signs were constant, it is reasonable to assume that there was no significant change in the rate of delivery of carbon dioxide to the lungs coincident with the start of nitrous oxide administration. Administration of nitrous oxide resulted in no elevation and even, on occasion, slight lowering of arterial blood pressure. The elevation of $P_{\text{ACO}_2}$ concomitant with nitrous oxide administration seen in this study could not have been substantially influenced by increased CO$_2$ delivery to the lungs.

The observation that the higher the concentration of nitrous oxide, the greater the increase in $P_{\text{ACO}_2}$ may be explained by the fact that the volume absorption of nitrous oxide in the lungs, and thus the concentrating effect, is greater with greater concentrations of nitrous oxide.

The results of the present study have also demonstrated that the lower the degree of ventilation, i.e., the higher the $P_{\text{ACO}_2}$ prior to introduction of nitrous oxide, the greater the second-gas effect (the greater rise in $P_{\text{ACO}_2}$) at a constant concentration of inspired nitrous oxide. As Stoepling and Eger5 have suggested, because the uptake of nitrous oxide is relatively unaffected by the differences in ventilation, the reduction in gas volume produced by the uptake of nitrous oxide is proportionally less as ventilation is increased.

The increase in $P_{\text{ACO}_2}$ observed in this study may reflect an increase in $P_{\text{ACO}_2}$ of even greater magnitude. Although there is normally no difference between alveolar gas and alveolar capillary blood $P_{\text{CO}_2}$'s mean arterial (a) and mean alveolar (A) CO$_2$ tensions may differ (Severingham13). This a-A gradient has been shown to be a function of the distribution of ventilation and perfusion.16-19 Askrog,18 for example, demonstrated the effect of hemodynamic changes on the ventilation-perfusion ratio by showing an increase in a-A $P_{\text{CO}_2}$ gradient due to a decrease in pulmonary arterial pressure. Lenfant19 produced an increase in a-A $P_{\text{CO}_2}$ gradient by increasing the concentration of inspired oxygen. In the present study, since arterial blood pressure was slightly lowered and the inspired oxygen concentration was increased by the administration of nitrous oxide, the a-A $P_{\text{CO}_2}$ gradient may well have increased during the administration of nitrous oxide.

Under desirable conditions ($P_{\text{ACO}_2}$'s of 40 torr or less), increases in $P_{\text{ACO}_2}$ following nitrous oxide administration are small, and can be controlled with additional ventilation. However, in the presence of pre-existing hypercarbia, the degree of increase in $P_{\text{ACO}_2}$ demonstrated in the present study would increase intracranial pressure significantly.20

The nitrous oxide analyzer was provided by Ayerst Corporation.

References


Neonatology

VENTILATION WITH CONTINUOUS POSITIVE PRESSURE AND NEONATAL RESPIRATORY DISTRESS Twenty infants with severe IRDS, defined as Pao2 of less than 50 torr when breathing 100 per cent oxygen or repeated episodes of apnea, bradycardia, and cyanosis on 70 to 100 per cent oxygen, were treated with a ventilatory pattern that included continuous positive airway pressure (CPAP). Sixteen of the 20 infants survived. In 18 infants, the positive airway pressure was applied with a modified T-piece arrangement and a screw-clamp on a reservoir bag to control pressures. A pressure monitor and a "pop-off" valve were included to prevent excessive pressures. All these infants' tracheas were intubated. In the other two cases, continuous positive airway pressure was applied by enclosing the infant's head in a chamber while pressure was controlled externally. Endotracheal intubation of these two infants was not necessary.

Initially, a pressure of 6 torr was applied to the airway; this was increased by increments of 2 to 12 torr as necessary, to achieve the desired Pao2. The inspired oxygen concentration was progressively decreased as tolerated. As clinical status improved, CPAP was diminished until oxygenation was maintained in its absence.

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