

## Nitrous-oxide-induced Diffusion Hypoxia in Patients Breathing Spontaneously

LCDR L. Sheffer, MC, USN,\* CDR J. L. Steffenson, MC, USN,†  
LCDR A. A. Birch, MC, USN ‡

The outflow of nitrous oxide at the end of anesthesia in patients breathing spontaneously and its effects on arterial blood gases and ventilatory drive were measured in eight healthy young patients. Nitrous oxide-methoxyflurane anesthesia at an inspired oxygen concentration of 20.9 per cent resulted in a significant decrease in  $P_{aO_2}$ . Maximum depression from control ( $69.4 \pm 12.5$  mm Hg) was seen at 2.5 minutes ( $54.3 \pm 11.2$  mm Hg).  $P_{aCO_2}$  decreased significantly from a high level during the control period ( $49.5 \pm 7.9$  mm Hg) to a near-normal value ( $41.9 \pm 7.1$  mm Hg) after 5 minutes of breathing air. These changes were seen when nitrous oxide outflow was greatest. Nitrous oxide outflow peaked at 1.5 minutes ( $1,033 \pm 377$  ml/min) and fell rapidly thereafter. At 11 minutes it was approximately half of the peak value ( $496 \pm 288$  ml/min). Oxyhemoglobin saturation tended to decrease, but ventilatory drive was not significantly changed. It is concluded that elimination of nitrous oxide will result in a lowering of  $P_{aO_2}$  which is potentially dangerous, and that during this time high inspired oxygen concentrations are indicated. (Key words: Nitrous oxide; Diffusion hypoxia;  $P_{aO_2}$ ; Ventilatory drive.)

DILUTION OF ALVEOLAR OXYGEN by nitrous oxide and nitrogen when a patient is made to breathe air at the end of anesthesia was ini-

tially reported by Fink *et al.* in 1954.<sup>1</sup> Several recent articles have dealt with this subject.<sup>2-4</sup> This began a trend toward administration of 100 per cent oxygen at the end of anesthesia with  $N_2O$  in order to prevent "diffusion hypoxia." Frumin and Edelist<sup>3</sup> recently suggested that although administration of high oxygen concentrations was probably beneficial, it was not necessary since no clinically significant desaturation of arterial blood occurred when patients were changed from an 80 per cent  $N_2O$  mixture to room air.

Others<sup>5-7</sup> have found that the movement of  $N_2O$  through the alveolar space washes out and dilutes alveolar  $CO_2$ , thereby lowering  $P_{aCO_2}$ . A decrease in ventilatory drive with hypoventilation would follow. It has been suggested that this is a second mechanism involved in the decrease of  $P_{aO_2}$ .

The present study was designed to demonstrate: 1) the overall effects of elimination of nitrous oxide on arterial oxygen tension, carbon dioxide tension and oxyhemoglobin saturation; 2) the absolute rate of  $N_2O$  outflow at the end of anesthesia; 3) the relationship between changes in  $P_{aCO_2}$  and ventilatory drive as reflected by inspiratory minute ventilation.

### Method

Eight patients, ages 19 to 40 years, were studied. All were free of cardiac and pulmonary disease. All underwent operations on extremities of two to three hours' duration. Anesthesia was induced with thiopental, followed by succinylcholine for intubation. No other muscle relaxant was used. Anesthesia was maintained with nitrous oxide, 78.5 per cent, and methoxyflurane, 0.6 per cent. This concentration of methoxyflurane was used to provide a relatively slow emergence from anesthesia with an even ventilatory pattern, thereby preventing large changes in functional residual

\* Third-year resident.

† Assistant Chief.

‡ Assistant Professor, Department of Anesthesiology, Bowman-Gray School of Medicine, Winston-Salem, N.C.

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Reprint address: LCDR L. Sheffer, MC, USN, c/o Director, Clinical Investigation Center, Naval Hospital, Oakland, California 94627.

capacity (FRC). It has been shown<sup>8,9</sup> that reductions in FRC may occur after induction of anesthesia; however, the changes are small and not progressive with time. No significant change in FRC occurs during emergence from anesthesia. To prevent any change in the inspired oxygen content at the end of anesthesia, oxygen, 20.9 per cent, was administered prior to converting the patient to breathing ambient air. This oxygen fraction was verified by measuring the  $P_{iO_2}$  of the inspired mixture with an Instrumentation Laboratory Model 113-127 Analyzer.

Because of the low solubility of nitrogen, we did not correct for nitrogen uptake after conversion to breathing of room air. This resulted in a small underestimate of nitrous oxide outflow.

An arterial cannula was placed in the radial artery and blood sampled just before conversion to room air (control), at the time of conversion (zero time), at 0.5, 1, 1.5, 2, 2.5, and 3 minutes, and at one-minute intervals thereafter.  $P_{aO_2}$ ,  $P_{aCO_2}$  and pH were measured with the IL analyzer within 45 minutes after storage of the blood on ice. From these data  $O_2$  saturation was calculated on a Severinghaus blood-gas calculator.

To measure ventilation, the patient inspired from one bell of a Godart Pulmotest respirometer through a "Sierra Y" one-way valve system into a bag-in-a-box. The expired volume displaced from the box was measured in the other bell of the respirometer. Specimens of mixed expired gas were collected for analysis of  $P_{O_2}$  and  $P_{CO_2}$  with the IL analyzer. Collections were made in the first 30 seconds of each minute; values are expressed in ml/min. These data, with the deadspace volume of the bag-in-a-box system (1,650 ml as determined by multiple helium-dilution measurements), were used to calculate  $CO_2$  output and  $O_2$  uptake. All volumes were measured at ambient pressure at 20 C and corrected to BTFS. The  $N_2O$  outflow was measured as the difference between inhaled and exhaled volumes after corrections were made for  $O_2$  uptake and  $CO_2$  output, and is reported as STPD. From  $CO_2$  output total alveolar ventilation was calculated.

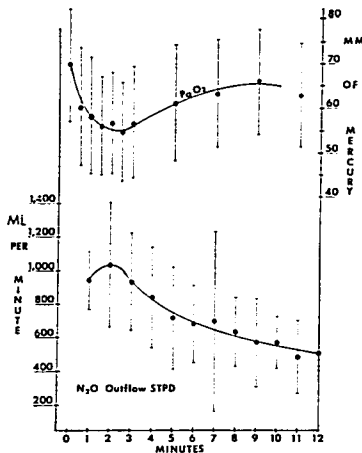


FIG. 1.  $P_{aO_2}$  and  $N_2O$  outflow rates. The greatest depression of  $P_{aO_2}$  occurred during the fastest outflow of  $N_2O$ , within the first 5 minutes. Each point represents the mean; the accompanying bar represents the standard deviation.

All probability levels were calculated by the two-tailed t test for paired differences, comparing the control values with subsequent values.

### Results

$P_{aO_2}$  began to decrease immediately on conversion to breathing of room air (fig. 1); the greatest depression, 15 mm Hg, occurred at 2.5 minutes.  $P_{aO_2}$  remained below control for the duration of the measurements (11 min), but values were significantly different from control only at 1, 1.5, 2, and 2.5 minutes. A 3.5 per cent decrease in  $O_2$  saturation occurred, but was not statistically significant.

The nitrous oxide outflow rate was highest during the first 3 minutes, correlating well with the period of greatest depression of  $P_{aO_2}$  (fig. 1). Peak outflow occurred at one minute ( $1,033 \pm 377$  ml/min).

An initial depression of mean inspired minute ventilation occurred, followed by an increase to above control (fig. 2). These changes

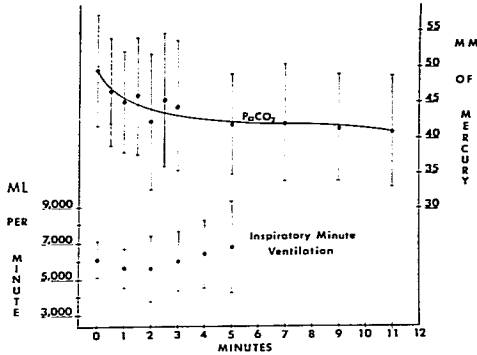


FIG. 2. Inspiratory minute ventilation and  $P_{aCO_2}$ . No significant change in inspiratory minute ventilation occurred, although  $P_{aCO_2}$  decreased. Each point represents the mean; the accompanying bar represents the standard deviation.

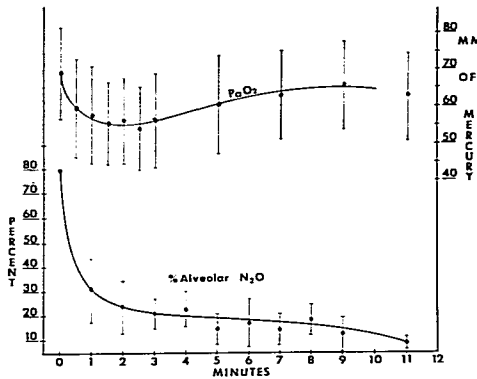


FIG. 3.  $P_{aO_2}$  and per cent alveolar nitrous oxide. The greatest depression of  $P_{aO_2}$  occurred early in the  $N_2O$ -washout phase, when alveolar  $N_2O$  concentration was highest. Each point represents the mean; the accompanying bar represents the standard deviation.

were not significant. However,  $P_{aCO_2}$  decreased steadily (fig. 2) as  $N_2O$  outflow increased alveolar ventilation.

Per cent alveolar  $N_2O$  concentration was calculated for each interval. Depression of  $P_{aO_2}$  correlated well with high alveolar  $N_2O$  concentration (fig. 3). Reversal of the decrease in  $P_{aO_2}$  occurred when the alveolar  $N_2O$  concentration was lowered.

#### Discussion

Frumin and Edelist suggested that "diffusion anoxia does not exist as a clinically sig-

nificant phenomenon . . . (in) . . . normal patients who awaken from  $N_2O$  anesthesia without respiratory irregularity or depression."<sup>3</sup> This statement was based on high arterial hemoglobin saturations seen in their patients, which had decreased only from 95.8 per cent (control) to 93.2 per cent 2 minutes after conversion to breathing of room air. Frumin and Edelist did not publish their control  $P_{aO_2}$  values. Hornbein<sup>4</sup> calculated them from the authors' data, and we have verified his calculations. Their patients had a 14-mm Hg decrease in  $P_{aO_2}$  at 2.5 minutes, which is nearly

identical to findings in our study. Because of the higher initial  $\text{Pa}_{\text{O}_2}$  in the Frumin-Edelist group, and the shape of the oxyhemoglobin-dissociation curve, we found a somewhat greater decrease in  $\text{O}_2$  saturation (3.5 per cent) in our patients.

One must bear in mind that these studies were done at an inspired  $\text{N}_2\text{O}$  concentration of 78.5 per cent. Using a 70 per cent  $\text{N}_2\text{O}$  mixture, the maximum decrease in  $\text{Pa}_{\text{O}_2}$  would still be about 13 mm Hg.

From these data, we conclude that a potentially hazardous decrease in  $\text{Pa}_{\text{O}_2}$  occurs during elimination of nitrous oxide after equilibration with 80 per cent nitrous oxide. This was seen in healthy, unobstructed, spontaneously-ventilating patients. The hazard is said to be potential, as it depends on at least four variables: 1) the initial or pre-washout  $\text{Pa}_{\text{O}_2}$  and its relation to the hemoglobin-dissociation curve; 2) the status of the respiratory system (disease states, anesthetic depression, etc.); 3) the capacity for carrying oxygen that an individual patient possesses (hemoglobin concentration, blood pH, cardiac output, temperature, etc.); 4) the patient's ability to withstand a hypoxic episode, which is essentially impossible to evaluate in advance. Unless an individual patient's  $\text{Pa}_{\text{O}_2}$  and ventilatory status are known, we believe he should receive 100 per cent  $\text{O}_2$  during  $\text{N}_2\text{O}$  washout to reduce the possibility of an untoward decrease in  $\text{Pa}_{\text{O}_2}$ .

The values for  $\text{N}_2\text{O}$  flow rates are in close agreement with predicted values on the basis of  $\text{N}_2\text{O}$  uptake studies by Severinghaus.<sup>10</sup> Our value of 20.5 per cent alveolar  $\text{N}_2\text{O}$  concentration at the 3-minute interval is in close agreement with the 24 per cent predicted by him and the values obtained in measurements of end-tidal nitrous oxide concentrations by Frumin *et al.*<sup>8</sup>

Finally, the relationship between the respiratory drive, as reflected by inspiratory mi-

nute ventilation, and  $\text{Pa}_{\text{CO}_2}$  is interesting. Although  $\text{Pa}_{\text{CO}_2}$  did decrease during the period of nitrous oxide outflow, there was no significant change in inspiratory minute ventilation. We believe, therefore, that the decrease in  $\text{Pa}_{\text{O}_2}$  seen during  $\text{N}_2\text{O}$  elimination results from dilution of alveolar oxygen.

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