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Respiratory Effects of Nitrous Oxide during Enflurane Anesthesia in Humans

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The authors measured resting ventilation, the ventilatory response to added CO_2, the V_D/V_T ratio, the rate of carbon dioxide output, and arterial P_{CO_2} in four healthy volunteers, awake and anesthetized with, in order (I) enflurane 0.4 MAC with nitrous oxide 70 per cent, (II) enflurane 1.1 MAC with nitrous oxide 70 per cent, and (III) enflurane 1.1 MAC alone. Enflurane 1.1 MAC reduced ventilation and the response to added CO_2 markedly, increased the V_D/V_T ratio, reduced rate of CO_2 output, and elevated values of Pa_{CO_2} from 41 ± 1 to 65 ± 3 mmHg (mean ± SEM). Enflurane 1.1 MAC with nitrous oxide 70 per cent had similar effects. Enflurane 0.4 MAC with nitrous oxide 70 per cent caused much smaller changes in each measured respiratory variable, increasing Pa_{CO_2} values to only 49 ± 1 mmHg. The results indicate that enflurane 1.1 MAC alone is too potent a depressant of alveolar ventilation to permit spontaneous breathing, but that the "equi-anesthetic" enflurane 0.4 MAC with nitrous oxide 70 per cent may not be. The magnitude of the beneficial respiratory effects of substituting nitrous oxide for an equivalent amount of vapor is substantially greater with enflurane than with either halothane or isoflurane. (Key words: Anesthetics, volatile: enflurane. Anesthetics, gases: nitrous oxide. Ventilation: dead space; CO_2 output; CO_2 response.)

IN THE ABSENCE of nitrous oxide or surgical stimulation, enflurane is a very potent depressant of ventilation in humans. Light levels of anesthesia (1.1 MAC) cause marked hypoventilation and hypercarbia, and deeper levels (2.0 MAC) produce apnea.[1] Even in the presence of concurrent surgical stimulation, enflurane alone produces unacceptably high levels of Pa_{CO_2}.[2] However, in clinical practice, inhalational anesthetics generally are administered with nitrous oxide, and it is known that substitution of nitrous oxide for a portion of halothane or isoflurane anesthesia results in somewhat less hypoventilation than is caused by equi-anesthetic doses of these vapors alone.[3,4]

The purpose of this study was to assess several respiratory variables when nitrous oxide 70 per cent was substituted for a portion of enflurane 1.1 MAC anesthesia, and also when nitrous oxide 70 per cent was added to it.

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Methods

The protocol of this study was reviewed and approved by the Health Sciences Standing Committee on Human Research at the University of Western Ontario. Each subject gave written consent to participate, after being informed of the nature of the proposed study and the risks involved, and after being examined for physical fitness by a physician not otherwise involved in the study. Four healthy male volunteers were accepted. Their ages were 32 ± 4 years, weights 71 ± 8 kg, and heights 178 ± 8 cm (means ± SD).

Subjects were studied in three steady anesthetic states in the following order: (I) enflurane 0.4 MAC with nitrous oxide 70 per cent; (II) enflurane 1.1 MAC with nitrous oxide 70 per cent; and (III) enflurane 1.1 MAC alone. Control awake values were obtained on a separate occasion, either prior to or at least one week following anesthesia. We assumed that enflurane MAC for our subjects was 1.68 per cent,[5] that the nitrous oxide 70 per cent MAC equivalent in anesthetic mixtures was 0.7 MAC,[5] and that anesthetic states (I) and (III) were equipotent.

All subjects, with overnight fast, unpremedicated, were positioned supine. Monitoring included systemic arterial blood pressure (Riva-Rocci method), electrocardiogram (limb lead II), and nasopharyngeal temperature. An intravenous infusion of 5 per cent dextrose in 0.2 per cent saline was started, and the rate of infusion was adjusted to maintain systolic blood pressure within 25 per cent of awake values during the course of the study.

After 3.0 mg *d*-tubocurarine, iv, anesthesia was induced with nitrous oxide and enflurane. With the aid of 1 mg/kg succinylcholine, iv, the trachea was intubated with a cuffed endotracheal tube, ID 8.0 or 8.5 mm. Following recovery from paralysis, the subject was allowed to breathe spontaneously from a non-rebreathing circuit.

An indwelling arterial cannula was inserted into either the radial or dorsalis pedis artery for continuous blood pressure monitoring and sampling of arterial blood. End-tidal concentrations of CO_2, enflurane, and nitrous oxide, and inspired minute ventilation were all monitored continuously and recorded. The inspired anesthetic mixture was adjusted to achieve an end-tidal enflurane concentration equivalent to 0.4 MAC (0.67 per cent), and an end-tidal nitrous oxide concentration of 65–70 per cent.

After a 30-min period for equilibration and an ad-

ditional 10 min of constant ventilation and steady levels of end-tidal CO_2, nitrous oxide, and enflurane, we recorded a 1-min period of resting ventilation and end-tidal CO_2 and anesthetic concentrations. Exhaled gases were collected in a Douglas Bag for 3 min to measure the rate of CO_2 output, and a blood sample was withdrawn from the arterial cannula for subsequent blood-gas analysis. Next, the ventilatory response to added CO_2 was measured using Read's rebreathing method,[6] modified as described in a previous communication.[7] Briefly, the subject's airway was connected to a total rebreathing circuit primed with CO_2 8–10 per cent, appropriate concentrations of nitrous oxide and enflurane, and remainder oxygen. After receiving three large positive pressure tidal volumes from this circuit, the purpose of which was to achieve rapid equilibration, the subject was allowed to breathe from it spontaneously and thereby accumulate CO_2. If the tracing of airway CO_2 concentration showed little or no variation throughout the respiratory cycle, and if end-tidal O_2 remained greater than 18 per cent, we permitted the test to proceed until the end-tidal CO_2 concentration had increased 1.7–2.0 per cent. At that point, the subject was returned to the non-rebreathing system.

Next, the inspired enflurane concentration was increased to produce an end-tidal concentration equivalent to 1.1 MAC (1.85 per cent), while nitrous oxide administration continued unchanged. After at least 30 min, and with ventilation and end-tidal CO_2 and anesthetic concentration again steady, the same measurements were repeated and recorded. Finally, nitrous oxide was discontinued while end-tidal enflurane concentration was maintained at the 1.1 MAC level (1.85 per cent), by adjusting the Ohio® enflurane vaporizer setting.[8] After a further 30 min during which end-tidal N_2O decreased to less than 3.0 per cent, an arterial sample was withdrawn for determination of arterial enflurane tension and the respiratory measurements were repeated once again.

The anesthetic time in each state, with some variations among the subjects, was approximately 45 min. In all cases the study was completed in three hours. In the awake state, measurements were made with the subject breathing through a mouthpiece and nostrils occluded by a noseclip.

Concentrations of carbon dioxide, nitrous oxide, and enflurane were measured with a Perkin-Elmer #1100® mass spectrometer, set in the "anesthetic"§ mode to minimize CO_2–N_2O interaction. Gas signals were calibrated each testing day with Canadian Liquid Air Specialty Gases, the CO_2 in the presence of N_2O, and N_2O in the presence of CO_2. The enflurane signal was checked regularly against calculated vapor concentrations of measured amounts of enflurane injected into a closed chamber of known volume, temperature, and pressure. Values of dried end-tidal concentrations were read from a time-based recording and were converted to tensions, using the measured barometric pressure of each testing day.

Samples of arterial blood for blood-gas analysis were capped and immediately placed on ice, and were analyzed within two hours using a calibrated Radiometer Copenhagen BMS III system, taking into account both memory and membrane effects on the oxygen electrode.

Arterial tensions of enflurane were determined by gas chromatography. A 5-ml portion of the heparinized arterial blood sample was equilibrated with an equal volume of air in a syringe which rotated in a water bath maintained at 37° C. After 45 min, the equilibrated gas phase was separated carefully from the blood and injected into the gas sampling loop of a Hewlett-Packard® Gas Chromatograph (#5730A), for measurement of its enflurane content. The blood sample was then reequilibrated with an equal volume of air three or four additional times and each of these equilibrated gas phase samples was also injected into the gas chromatograph. The chromatograph column had been packed with Carbopack "B" coated with SE-30 0.8 per cent and was maintained at 170° C. The column effluent was analyzed with a flame ionization detector. Peak heights, which had been calibrated with our enflurane standards, were inscribed on a time-based recorder. A plot of log peak heights *vs.* sample number yielded a straight line with a negative slope, whose intercept on the Y axis represented the concentration of enflurane in the gas phase which, in equilibration with blood, would have produced the original blood level.¶ Intercept concentrations from duplicate samples were averaged and this value was converted to enflurane tension.

Inspired tidal volume was measured by pneumotachography with the pneumotachograph head incorporated in the inspiratory limb of each circuit employed. The integrated signal (volume) was calibrated regularly with an air calibration syringe, and correction factors previously determined by calibrating with various gas mixtures, were applied for the density and viscosity of the respective inhaled gas mixture. Each value of resting ventilation was the average of a 1-min recording of ventilation. Values of instantaneous ventilation during the CO_2 response were the averages of at least three consecutive breaths. CO_2 output was computed from values of resting ventilation and the difference between inhaled and mixed exhaled CO_2 concentration. Volumes of ven-

§ N_2O interferes with the reading of CO_2 in the mass spectrometer; the anesthetic mode is designed to eliminate this interference.

¶ McAullife C: G C determination of solutes by multiple phase equilibration. Chem Tech:46–51, 1971.

TABLE 1. Effects of Nitrous Oxide during Enflurane Anesthesia

State	Pa_{CO_2} (mmHg)	$P_{ET_{CO_2}}$ (mmHg)	$\dot{V}_I$ BTPS ($l \cdot min^{-1}$)	V_T (l)	f (breaths/min)	CO_2 Response Slope ($l \cdot min^{-1} \cdot mmHg^{-1}$)	V_D/V_T*	$\dot{V}_{CO_2}$ STPD ($l \cdot min^{-1}$)
Awake	41 ± 1	41 ± 1	6.48 ± 0.75	0.62 ± 0.06	11 ± 1	2.13 ± 0.55	0.36 ± 0.04	0.19 ± 0.02
1) Enflurane 0.4 MAC with N_2O 70 per cent	49 ± 1	42 ± 1	5.05 ± 0.34	0.30 ± 0.04	17 ± 1	0.89 ± 0.14	0.47 ± 0.02	0.15 ± 0.01
2) Enflurane 1.1 MAC with N_2O 70 per cent	66 ± 2	53 ± 2	3.33 ± 0.23	0.18 ± 0.01	18 ± 1	0.40 ± 0.11	0.63 ± 0.05	0.09 ± 0.01
3) Enflurane 1.1 MAC	65 ± 3	52 ± 3	3.68 ± 0.40	0.24 ± 0.02	15 ± 1	0.50 ± 0.25	0.59 ± 0.02	0.11 ± 0.01
Statistical Comparison†								
Awake-1	0.05	NS	0.05	0.01	0.01	0.05	0.05	NS
Awake-2	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.05
Awake-3	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.05
1-2	0.01	0.01	0.05	0.05	NS	NS	0.01	0.05
1-3	0.01	0.01	0.05	NS	NS	NS	0.05	0.05
2-3	NS	NS	NS	NS	NS	NS	NS	NS

Values are means ± SEM; n = 4.
* Includes mechanical deadspace 25 ml.
† Statistical values denote P less than stated; NS indicates $P > 0.05$.

tilation were expressed at BTPS, and volumes of CO_2 output at STPD.

To analyze ventilatory responses to added CO_2, we assumed a linear relationship between ventilation and $P_{ET_{CO_2}}$, and computed the slope and intercept of the least-squares linear regression.

The V_D/V_T ratio was calculated using the modified Bohr's equation[9];

$$V_D/V_T = \frac{Pa_{CO_2} - \bar{PE}_{CO_2}}{Pa_{CO_2}}$$

In all conditions, this ratio was determined in the presence of an added external mechanical deadspace of approximately 25 ml, and during anesthesia with an endotracheal tube in place.

To determine possible differences between states, we employed analysis of variance for the four states and considered P values of 0.05 or less as statistically significant.

Results

Except for the subjective effects of hypercarbia in all subjects while awake, and nausea and vomiting following anesthesia in three, there were no complications related to these studies. Mean blood pressure (*i.e.*, diastolic plus 1/3 systolic − diastolic difference) while awake and in anesthetic states I, II, and III were respectively 88 ± 5, 74 ± 6, 67 ± 2, and 69 ± 2 mmHg (means ± SEM), respectively. Heart rates for the same conditions were 69 ± 10, 76 ± 8, 86 ± 6, and 94 ± 7 beats/min (means ± SEM), respectively. Measured arterial blood P_{O_2} values always exceeded 86 mmHg. Nasopharyngeal temperatures during anesthesia were at all times 35.5° C or greater. Total intravenous fluids administered during anesthesia to maintain normotension ranged from 1,300 to 2,900 ml.

Steady respiratory and anesthetic states were achieved with ease. During enflurane 1.1 MAC anesthesia, arterial blood tensions of enflurane were close to end-tidal, 12.1 ± 0.7 mmHg and 12.6 ± 0.5 mmHg, respectively. Average difference between duplicate means in blood tension was 0.9 mmHg.

The principle observations of the study are tabulated in the table and displayed in figure 1. Compared to the awake state, all anesthetic states increased Pa_{CO_2} considerably, reduced ventilation and tidal volume, decreased the CO_2 response slope, displaced the CO_2 response curve to the right (as assessed by the calculated intercept), and increased the V_D/V_T ratio (all P values < 0.05). With the exception of State 1, $\dot{V}_{CO_2}$ was reduced also and $P_{ET_{CO_2}}$ increased significantly (all P values < 0.05). All anesthetic states resulted in an end-tidal to arterial P_{CO_2} gradient, accounting for the small increase in $P_{ET_{CO_2}}$ in State 1 from the awake state.

There were no significant differences between enflurane 1.1 MAC alone (III) and enflurane 1.1 MAC with nitrous oxide 70 per cent (II). However, comparing enflurane 0.4 MAC with nitrous oxide 70 per cent (I) to enflurane 1.1 MAC alone (III), the enflurane–nitrous oxide mixture increased minute ventilation, reduced Pa_{CO_2} markedly, and shifted the CO_2 response curve to the left (all P values < 0.05). The slope of the CO_2 response also exhibited a trend towards improvement. In addition, the nitrous oxide combination reduced the V_D/V_T ratio and increased the rate of CO_2 output (both P values < 0.05). This higher rate of CO_2 output made the reduction in Pa_{CO_2} values less than expected from the observed differences in minute ventilation and V_D/V_T

ratio. Similar difference was observed between enflurane 0.4 MAC with N_2O 70 per cent and enflurane 1.1 MAC with N_2O 70 per cent.

Values of the V_D/V_T ratio correlated inversely with tidal volume considering data pooled from all anesthetic states ($r = -0.81$, $P < 0.01$).

Analysis of data after completion of the study in four subjects indicated that the differences between States I and III were large and significant. It was felt that our basic questions had been answered and that additional studies would serve no meaningful purpose and were ethically unjustified. Thus, the study was limited to four subjects.

Discussion

Nitrous oxide is a basal anesthetic agent which traditionally has been considered relatively inert, causing little physiologic disturbance other than its anesthetic effect. However, recent studies have demonstrated that, alone or in combinations with other agents, nitrous oxide may have considerable stimulant or depressant effects on a number of cardiovascular and respiratory variables.[3,10-15]**

We wondered about important respiratory effects of nitrous oxide during enfluranne anesthesia, as our clinical experience suggested that nitrous oxide–enflurane mixtures could be satisfactory for spontaneous breathing, even though enflurane alone was clearly not.[2] Accordingly, we compared the respiratory effects of enflurane 1.1 MAC alone (III) to the effects of two-enflurane–nitrous oxide combinations; enflurane 0.4 MAC with nitrous oxide 70 per cent (I)—representing an approximately "equi-anesthetic" substitution of N_2O, and enflurane 1.1 MAC with nitrous oxide 70 per cent (II)—representing an addition of N_2O.

Because of the reported adaptation of enflurane-induced ventilatory depression with time,[1] we studied the enflurane–nitrous oxide combinations first and enflurane alone last. Should time-related adaptation have occurred, our results would have tended to underestimate the ventilatory depressant effect of the vapor alone which was studied last, and therefore underestimate any beneficial effects of substituting or adding N_2O.

To render end-tidal anesthetic levels a reasonable index of anesthetic dose and to measure respiratory variables in a steady state, we allowed at least thirty minutes for equilibration to each new state and ensured that ventilatory and end-tidal values of CO_2, nitrous oxide, and

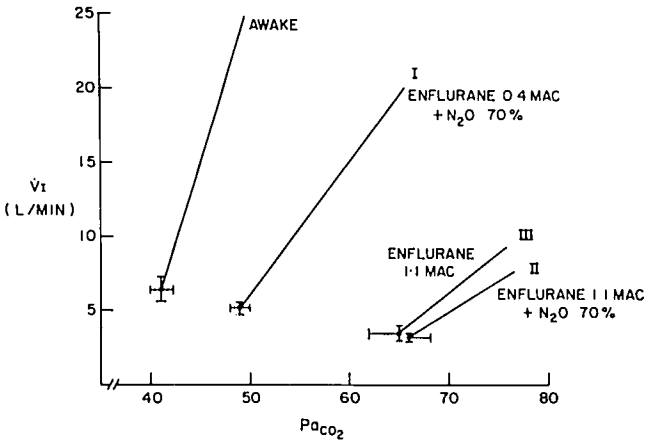

FIG. 1. Ventilation, Pa_{CO_2} values, and ventilatory responses to added CO_2 during all four states studied. Dots represent mean values of resting ventilation and Pa_{CO_2}, with bars indicating standard errors of the mean. Lines extending from the dots depict mean slopes of CO_2 response curves. Note that adding nitrous oxide 70 per cent to enflurane 1.1 MAC (compare States II and III) had little or no ventilatory effect. However, substituting nitrous oxide (compare States I and III) increased ventilation, reduced Pa_{CO_2} markedly, and shifted the CO_2 response curve to the left.

enflurane were all constant for ten minutes before measurements were made. During enflurane 1.1 MAC alone, end-tidal tensions of enflurane were quite close to arterial tensions.

Consistent with previous studies, enflurane 1.1 MAC alone caused profound ventilatory depression (table 1).[1,2,7] The addition of nitrous oxide 70 per cent (*i.e.*, enflurane 1.1 MAC + N_2O 70 per cent) produced no additional effects. However, substituting nitrous oxide 70 per cent for an "equi-anesthetic" portion of enflurane (*i.e.*, enflurane 0.4 MAC with N_2O 70 per cent) resulted in greater ventilation (table 1). In association, the ventilatory response to added CO_2 was displaced to the left (fig. 1) and Pa_{CO_2} was reduced considerably, from 65 ± 3 mmHg to 49 ± 1 mmHg (table 1).

The reduction of Pa_{CO_2} values associated with substituting nitrous oxide was the result of changes in all three determinants of Pa_{CO_2}, whose relationship is described by the following equation.[16]

$$Pa_{CO_2} = K \frac{\dot{V}_{CO_2}}{\dot{V}_E\left(1 - \frac{V_D}{V_T}\right)}$$

where $\dot{V}_{CO_2}$ = CO_2 output; $\dot{V}_E$ = expired minute ventilation; V_D/V_T = ratio of deadspace to tidal volume; and K = a constant. Enflurane 0.4 MAC with nitrous oxide 70 per cent not only increased ventilation,†† but reduced

** Winter PM, Hornbein, TF, Smith, et al: Hyperbaric nitrous oxide anesthesia in man: Determination of anesthetic potency (MAC) and cardiorespiratory effects. American Society of Anesthesiologists (Abstracts) 103–104, 1972

†† In this discussion, we have ignored the small difference between inspired and expired minute ventilation.

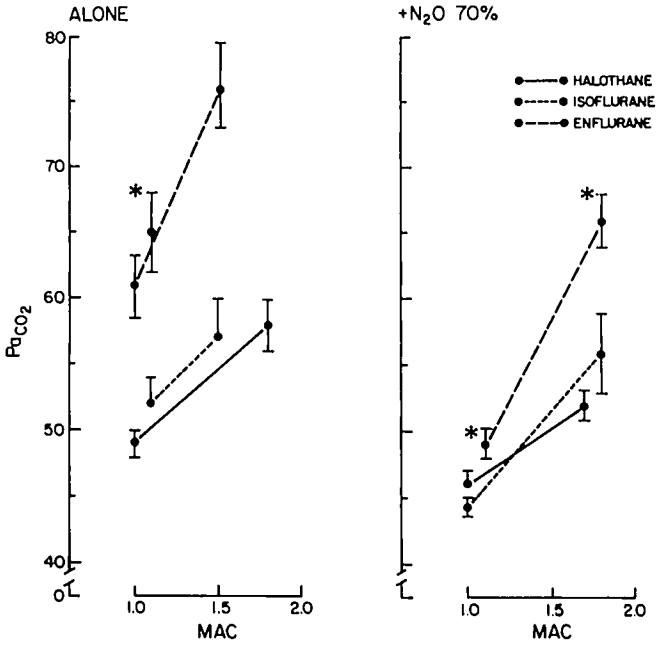

FIG. 2. Pa_{CO_2} values, means ± SEM, at various MAC doses of halothane, isoflurane, and enflurane and anesthesia, alone (*left*) and with nitrious oxide 70 per cent included (*right*). At 1.0–1.2 MAC, enflurane alone produces much higher values of Pa_{CO_2} than halothane or isoflurane alone. With the inclusion of nitrous oxide, all Pa_{CO_2} values decrease and the differences between agents lessen, especially at 1.0–1.2 MAC. (Halothane data are from Hornbein *et al.*,[3] isoflurane data from Eger *et al.*,[4] enflurane data indicated by an asterisk are from the present study, and remaining enflurane data are from Calverley et al.[1])

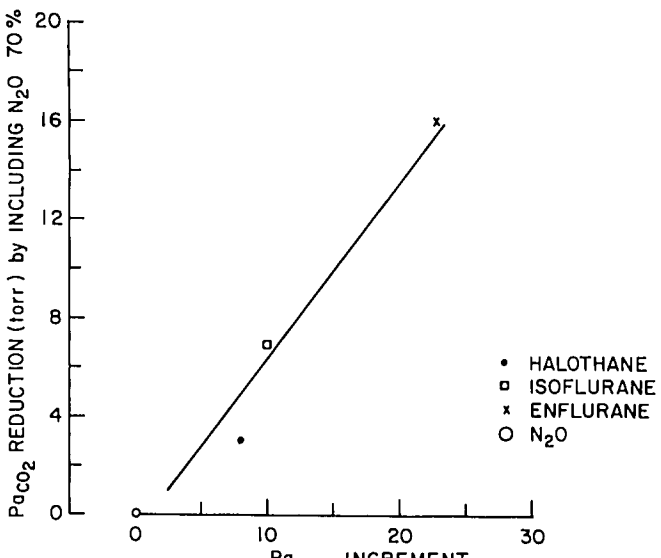

FIG. 3. The mean effect on Pa_{CO_2} of substituting nitrous oxide 70 per cent for an equi-anesthetic portion of halothane, isoflurane, and enflurane 1.0–1.1 MAC. The greater the Pa_{CO_2} increment caused by the vapor agent alone, the greater the Pa_{CO_2} reduction gained by substituting N_2O ($r = 0.98$). (Halothane data are from Hornbein *et al.*,[3] isoflurane data from Eger *et al.*,[4] enflurane data from the present study, and nitrous oxide data from Winter *et al.*, ASA abstracts, 103–104, 1972.)

the V_D/V_T ratio and increased the rate of CO_2 output at the lungs (table 1). The increased ventilation and reduced V_D/V_T ratio acted to decrease Pa_{CO_2}, each contributing proportionately the same to this beneficial effect, but were offset to some extent by the increased rate of CO_2 output. The CO_2 output was surprisingly low in all states, raising the question whether steady states were achieved, though care had been taken to ensure that adequate time was allowed for equilibration, and that the exhaled gases were only collected when steady levels of end-tidal CO_2, nitrous oxide, and enflurane had been established. The progressive decrease in CO_2 output with increasing anesthetic depth (from State I to II), on the other hand, was not unexpected and had been observed with halothane and isoflurane.[17] It was not our primary intent to investigate the metabolic rate associated with the different anesthetic states; hence, rates of oxygen consumption were not measured.

What are the mechanisms for each of these effects of substituting nitrous oxide, *i.e.*, increased ventilation, reduced V_D/V_T ratio, and increased rate of CO_2 output? The augmented volume of ventilation could have been in part due to the reduced inspired oxygen concentration associated with the use of N_2O; however, this seems unlikely as patients anesthetized with enflurane have virtually no ventilatory response to variation of end-tidal oxygen tension between 400 and 45 mmHg.[7] An attractive explanation is simply that enflurane alone is a ventilatory depressant, even in subanesthetic doses,[7] while nitrous oxide alone is a mild ventilatory stimulant, and that replacement of a portion of the depressant agent with the mild stimulant produces better ventilation. This assumes that when combined, there is no important interactive effect between the two. We observed that at enflurane 1.1 MAC adding nitrous oxide 70 per cent had no discernible ventilatory effect (table 1, fig. 1), but this does not exclude interaction at the lower enflurane dose of 0.4 MAC.

Although not statistically significant, there was a clear trend towards larger tidal volumes from State III to State I, and the reduced V_D/V_T ratio associated with substitution of nitrous oxide may have been related to a larger tidal volume. In spontaneously breathing anesthetized subjects, V_D/V_T ratios have been reported to vary inversely with V_T,[18] and our observations confirm a negative correlation between the two. The increased rate of CO_2 output at the lungs, which in the steady state reflects a higher rate of metabolic production of CO_2, may relate to the reported sympathomimetic effects of nitrous oxide in the presence of other anesthetics.[11]

Each of these N_2O-induced effects might have been better understood if we had been able to study enflurane 0.4 MAC alone. However, this was impossible as subjects given this dose of enflurane tend to be restless and excitable and therefore not in a steady state.

The benefit in terms of Pa_{CO_2} of substituting nitrous oxide 70 per cent for an equi-anesthetic portion of enflurane was clearly greater with enflurane than what was reported previously with isoflurane and with halothane (fig. 2).[3,4] Indeed, we observed a quantitative relationship between the Pa_{CO_2} increment produced by a 1.0–1.1 MAC dose of each of four inhalational anesthetics and the P_{CO_2} reduction associated with substituting nitrous oxide 70 per cent for an equi-anesthetic portion of each (fig. 3). Although enflurane alone is a considerably greater ventilatory depressant than isoflurane alone, and isoflurane alone a slightly greater depressant than halothane alone, the inclusion of nitrous oxide 70 per cent minimizes the Pa_{CO_2} differences among them, and this is especially so at the light levels of anesthesia commonly employed in clinical practice (*i.e.*, 1.0–1.2 MAC) (fig. 2).

The findings of the present study indicate that for adequate spontaneous ventilation during light enflurane anesthesia in normal man, it is necessary to include nitrous oxide in the anesthetic mixture. If enflurane must be administered by itself, it would seem prudent to control ventilation routinely. While the present study did not address potential modifying effects of surgical stimulation, the usual net effect of surgery during anesthesia is to reduce Pa_{CO_2} values 5–10 mmHg, a magnitude of effect which has been observed with enflurane alone,[2] and seems to be relatively independent of anesthetic agent and dose, with or without N_2O.[2,4,17] Thus, healthy patients undergoing surgery with enflurane 0.4 MAC and N_2O 70 per cent should have Pa_{CO_2} values in the range of 40–50 mmHg, similar to values observed with other N_2O–vapor and N_2O–narcotic–vapor mixtures.

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