Impact of Nitrous Oxide on the Circulation during Enflurane Anesthesia in Man

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Cardiovascular effects of nitrous oxide during enflurane anesthesia were studied in 12 healthy, young volunteer subjects ventilated to maintain normal Pa_{CO_2}. Twelve circulatory variables were measured and 13 more calculated. When nitrogen, 70 per cent, was added to enflurane, 1.86 per cent (1 MAC), or enflurane, 2.93 per cent end-tidal, no change was observed. When nitrous oxide, 70 per cent, was added, only minimal changes were observed. In a second part of the study, enflurane was compared with enflurane–nitrous oxide, 70 per cent, at equipotent levels. The following three variables (in percentages) decreased less in relation to awake control values at 1 MAC enflurane–nitrous oxide–oxygen than at 1 MAC enflurane–oxygen: left ventricular stroke work, −47.2 vs. −55.9; aortic dP/dt, −44.0 vs. −57.1; pressure–pulse product, −26.6 vs. −39.4. Forearm venous compliance decreased more: −26.0 vs. 2.9. The difference between the anesthetic mixtures was much more noticeable at 1.5 MAC, where eight variables (in percentages) decreased less with enflurane–nitrous oxide–oxygen than with enflurane–oxygen: cardiac output, −6.9 vs. −22.1; stroke volume, −31.4 vs. −46.0; left ventricular minute work, −32.6 vs. −49.6; left ventricular stroke work, −50.8 vs. −65.8; left ventricular stroke power, −48.2 vs. −63.1; ballistocardiogram, −34.5 vs. −49.1; aortic dP/dt, −49.7 vs. −65.8; pressure–pulse product, −32.3 vs. −42.3. Heart rate increased less when nitrous oxide was included in the mixture: 34.5 vs. 43.6. The lack of response during the addition of nitrous oxide to enflurane–oxygen is contrary to the significant sympathomimetic response seen when nitrous oxide is added to halothane, fluroxene, or diethyl ether. The apparent protection afforded by nitrous oxide at equipotent anesthetic levels is small enough that the main consideration in choosing between the two mixtures should be the concentration of oxygen needed by the patient. (Key words: Anesthetics, gases, nitrous oxide; Anesthetics, volatile, enflurane; Heart, cardiac output; Heart, myocardial function; Heart, contractility; Blood pressure, peripheral vascular resistance; Interactions, drug.)

FOR THE FIRST 100 YEARS or more of its anesthetic existence, nitrous oxide was viewed as a benign, bland

substance; something with which to dilute oxygen and, perhaps, to provide a modicum of baseline anesthesia. Within the past ten years, however, nitrous oxide has been shown to have significant effects on the central nervous, cardiovascular, and respiratory systems.[1–7] These effects can vary considerably and depend on many factors, such as the background anesthetic agent. For example, circulatory stimulation[2–4] or depression[5,6]** may result. When added to inhalational anesthetic agents such as halothane, ether, or fluroxene, in healthy subjects, nitrous oxide usually produces an *alpha*-adrenergic-like response,[2–4] although with fluroxene[3] a response characteristic of stimulation of the *beta*-adrenergic system also appears. In the present study we examined the interaction of nitrous oxide with enflurane, an increasingly popular agent. Our results shows that the addition of nitrous oxide to enflurane has minimal effect. When enflurane–oxygen is compared with enflurane–nitrous oxide, 70 per cent–oxygen at equipotent levels, the latter is less depressant to the circulation. These findings are particularly important because of the marked circulatory depression and the narrow margin of safety associated with enflurane alone.††

Methods

Twelve healthy male volunteer subjects ranging in age from 21 to 25 years were studied. The Human Investigation Committees of the University of California, San Diego, and the Veterans Administration Hospital, San Diego, approved the protocol and the consent procedures. After a thorough explanation, a detailed informed consent was obtained from each subject. Our methods have been described in detail,[2,8] and are summarized here, along with subsequent modifications.

Each subject arrived early in the morning, following a 12-hour fast. Using local anesthesia, we placed catheters into the brachial or axillary arteries and into the central venous system via an antecubital vein. The

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** Lunn JK, Hodges MR, Bidwai AV, et al: Cardiovascular effects of nitrous oxide during meperidine infusion in the dog (abstr). American Society of Anesthesiologists Annual Meeting, 1976, pp 369–370.

†† Calverley RK, Smith NT, Prys-Roberts C, et al: Cardiovascular effects of prolonged enflurane anesthesia in man (abstr). American Society of Anesthesiologists Annual Meeting, 1975, pp 57–58.

following variables were recorded continuously[2,8]: arterial and central venous pressures; a CM-5 lead of the electrocardiogram, the phonocardiogram (Sanborn microphone); end-tidal carbon dioxide and enflurane concentrations (Beckman LB-2 infrared analyzers), and skin (hand) and oral or esophageal temperatures by thermistors. The ultralow-frequency ballistocardiogram was recorded continuously whenever the bed was not being touched. Cardiac output (dye-dilution, with a Lyons densitometer and computer), arterial blood pH, P_{CO_2}, and P_{O_2} (Radiometer electrodes), forearm and finger blood flows (venous occlusion plethysmography), and pupillary diameter (Bausch and Lomb graduated magnifying lens) were measured intermittently. Most measurements were recorded on two Hewlett-Packard oscillographs, and several were recorded on a Hewlett-Packard magnetic tape recorder. Fifteen other variables were calculated from these measurements[2]: heart rate, stroke volume, left ventricular minute work, left ventricular stroke work, left ventricular stroke power, left ventricular ejection time, ejection time index, mean rate of left ventricular ejection, pre-ejection period (PEP), 1/(PEP), 1/(PEP)^2, aortic dP/dt, pressure–pulse product, forearm vascular resistance, and forearm venous compliance. The first derivative of arterial pressure (dP/dt) was obtained via a calibrated Hewlett-Packard Derivative Computer. Filtering of the output was accomplished at 50 Hz (−3 dB) at a roll-off of 12 dB.

Anesthesia was induced and maintained with enflurane–oxygen. No other anesthetic agent was given. Ventilation was controlled via a cuffed endotracheal tube to maintain Pa_{CO_2} within 2 torr of the awake value (mean value awake = 33 torr). Three hours of anesthesia with enflurane–oxygen preceded the initial observations with nitrous oxide. End-tidal enflurane concentration and cardiovascular values were stable for one hour prior to the addition of nitrous oxide.

The cross-over effect of nitrous oxide on the infrared enflurane analyzer was determined daily by concentration–response calibration. The resulting number was subtracted from the reading on the analyzer. Inspired oxygen concentration was measured with a fuel-cell analyzer (Biomarine).

Two types of studies were performed.

Group I. The enflurane–oxygen mixture was changed to enflurane and nitrogen–oxygen, 70:30 per cent, and thence to enflurane and nitrous oxide–oxygen, 70:30 per cent. The intervening step introducing nitrogen was added to elicit any possible response to a change in Pa_{O_2} without an alteration of anesthetic depth. These changes were accomplished at 1 MAC (1.86 per cent end-tidal enflurane concentration in subjects of this age[9]) (five subjects) or 1.5 MAC (2.79 per cent end-tidal) (six subjects) enflurane. In a seventh subject at 1.5 MAC, nitrous oxide was dis-

continued because of significant hypotension. In all cases, end-tidal concentration of enflurane was kept constant. Measurements were taken before any change in concentration, and after 15 min of administration of each mixture.

Group II. In six subjects we examined the cardiovascular effects of mixtures of enflurane and nitrous oxide–oxygen, 70:30 per cent. In this group the *total* MAC was calculated from the concentrations of enflurane and nitrous oxide. Thus, to achieve 1 MAC, we assumed that nitrous oxide, 70 per cent, was equivalent to 2/3 MAC[1,10]‡‡ and therefore combined nitrous oxide with enflurane, 0.63 per cent end-tidal. After measurements were made at this concentration, we increased the concentration to 1.5 MAC by adding enflurane, 0.93 per cent end-tidal. When possible, we subsequently increased the total concentration to 2 MAC enflurane–nitrous oxide–oxygen. On two of six occasions, we were unable to continue this mixture because of significant hypotension. Since we were rarely able to achieve 2 MAC with enflurane–oxygen alone, we are not reporting the data at this level.

Thus, we attained a dose–response curve for the combination of nitrous oxide–enflurane and compared these results with those obtained with enflurane–oxygen alone. Because duration of anesthesia significantly changes the circulatory impact of enflurane,†† we interpolated the enflurane–oxygen data from measurements made before and after the nitrous oxide administration. We assumed that any changes with time were linear.[11]

All data were analyzed with Student's t tests for paired or unpaired data. We accepted as significant P levels below 0.05.

Results

Esophageal (mean value awake = 36.3 C) and skin (mean value awake = 32.6 C) temperatures remained constant after both nitrogen and nitrous oxide had been added. Pupillary diameter (mean value awake = 5.0 mm) did not change from the awake to the anesthetized state, or when nitrous oxide was added to enflurane–oxygen.

Decreasing the concentration of oxygen by substituting nitrogen had no effect upon the circulation. The addition of nitrous oxide to enflurane–oxygen anesthesia did produce changes, but these were few and minimal. At enflurane, 1.86 per cent end-tidal (1 MAC), finger blood flow decreased (−41.2 ± 13.3 per cent, SEM), while at enflurane, 2.79 per cent, heart rate increased (+16.6 ± 2.9 per cent), and forearm

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

TABLE 1. Comparison of Enflurane-O_2 and Enflurane-N_2O-O_2 at Equivalent Concentrations*

	1 MAC			1.5 MAC		
	Per Cent Change from Awake Control ± SEM		Significance of Difference between the Two Mixtures	Per Cent Change from Awake Control ± SEM		Significance of Difference between the Two Mixtures
	Enflurane-O_2	Enflurane-N_2O-O_2		Enflurane-O_2	Enflurane-N_2O-O_2	
Cardiac output	−16.5 ± 8.6	−8.9 ± 10.7	NS	−22.1 ± 10.5	−6.9 ± 10.5	$P < 0.05$
Heart rate	32.6 ± 7.3	29.5 ± 9.7	NS	43.6 ± 7.1	34.5 ± 7.5	$P < 0.05$
Stroke volume	−37.7 ± 4.2	−30.3 ± 3.6	NS	−46.0 ± 5.1	−31.4 ± 5.1	$P < 0.01$
Mean arterial pressure	−30.0 ± 3.3	−24.0 ± 5.8	NS	−38.3 ± 4.0	−29.0 ± 4.9	NS
Mean central venous pressure (Δ torr)	1.1 ± 0.8	0.9 ± 1.4	NS	3.4 ± 0.8	1.6 ± 1.3	NS
Systemic vascular resistance	−16.4 ± 4.6	−16.9 ± 7.4	NS	−26.1 ± 4.8	−25.9 ± 5.4	NS
Left ventricular minute work	−39.7 ± 8.3	−29.6 ± 11.1	NS	−49.6 ± 8.0	−32.6 ± 9.8	$P < 0.05$
Left ventricular stroke work	−55.9 ± 4.3	−47.2 ± 4.6	$P < 0.01$	−65.8 ± 4.8	−50.8 ± 5.6	$P < 0.01$
Left ventricular stroke power	−51.8 ± 5.6	−45.2 ± 5.7	NS	−63.1 ± 5.6	−48.2 ± 6.4	$P < 0.01$
IJ-wave amplitude of utralow frequency acceleration of ballistocardiogram	−35.4 ± 7.3	−33.0 ± 6.6	NS	−49.1 ± 6.3	−34.5 ± 6.7	$P < 0.05$
Aortic dP/dt	−57.1 ± 6.2	−44.0 ± 5.6	$P < 0.005$	−65.8 ± 5.4	−49.7 ± 4.8	$P < 0.005$
Pre-ejection period (PEP)	12.9 ± 5.0	13.4 ± 4.9	NS	15.0 ± 6.0	13.8 ± 5.3	NS
$\frac{1}{(PEP)^2}$	−14.7 ± 6.9	−20.3 ± 7.1	NS	−19.5 ± 10.0	−20.4 ± 8.0	NS
Ejection time index	3.0 ± 1.3	5.2 ± 1.4	NS	6.9 ± 1.4	5.5 ± 1.7	NS
Mean rate left ventricular ejection	−32.6 ± 5.6	−28.1 ± 4.4	NS	−42.5 ± 5.9	−28.2 ± 5.7	NS
Pressure-pulse product	−35.4 ± 2.1	−26.6 ± 4.7	$P < 0.05$	−42.3 ± 2.8	−32.3 ± 3.7	$P < 0.01$
Finger blood flow	10.2 ± 22.0	97.2 ± 47.4	NS	48.3 ± 29.2	67.9 ± 25.7	NS
Forearm blood flow	19.5 ± 20.8	105.4 ± 47.5	NS	54.6 ± 16.2	107.0 ± 60.3	NS
Forearm vascular resistance	−38.3 ± 6.5	−55.0 ± 8.2	NS	−43.8 ± 4.7	−59.7 ± 7.5	NS
Forearm venous compliance	2.9 ± 17.0	−26.0 ± 12.3	$P < 0.05$	−6.8 ± 16.9	12.1 ± 29.4	NS

* The numbers listed are percentage changes from awake control values. Thus, a smaller negative number indicates relatively less depression.

venous compliance decreased (−32.1 ± 8.6 per cent). Pooling the data did not increase the number of significant changes: heart rate increased (11.8 ± 3.1 per cent), and forearm vascular compliance decreased (−26.6 ± 10.1 per cent). Given our assessment of 20 variables, we could have achieved one "significant" ($P < 0.05$) change purely by chance.

At both 1 MAC and 1.5 MAC there was less circulatory depression with the enflurane-nitrous oxide mixture than with enflurane alone (table 1). Left ventricular stroke work, aortic dP/dt, and pressure-pulse product evidenced less depression with enflurane-nitrous oxide-oxygen at 1 MAC. The difference between the anesthetic mixtures was more apparent at 1.5 MAC, where nine variables were involved: cardiac output, heart rate, stroke volume, left ventricular minute work, left ventricular stroke work, left ventricular stroke power, the IJ wave of the ballistocardiogram, aortic dP/dt, and the pressure-pulse product.

Discussion

ADDITION OF NITROUS OXIDE (GROUP 1)

The responses to nitrous oxide, such as they were, were not due to a change in oxygen concentration, as demonstrated by the lack of response to the addition of nitrogen. The usual circulatory response to decreased oxygen concentration is an increase in cardiac output and heart rate, and a decrease in systemic vascular resistance.[12] Although Price et al. observed no attenuation of this response in spontaneously ventilating subjects during halothane anesthesia, they did see an elimination of the response when ventilation was controlled.[12] Apparently enflurane has the same effect as halothane during controlled ventilation.

Not reflected by the data generated from the Group I studies is the one occasion on which nitrous oxide had to be discontinued shortly after its addition because of significant circulatory depression. Had this study been completed, it would very probably not have influenced the statistical results, except perhaps with stroke volume, since most of the variables tended to increase after addition of nitrous oxide. With or without this study, our conclusion remains the same: nitrous oxide does not stimulate the cardiovascular system in the presence of enflurane as it does in the presence of other potent inhalational agents.

The addition of nitrous oxide, 70 per cent, to enflurane anesthesia, in contrast to anesthesia with other inhalational anesthetic agents, produces little cardiovascular response at either light or deep levels. With

enflurane, one of 20 variables responded at light levels of anesthesia, while two of 20 responded at deep levels. With halothane, the respective numbers were five of 18 and six of 18; with diethyl ether, zero of 16 and five of 16; with fluroxene, eight of 18 and 11 of 18. Pooling the data obtained at light and deep levels with these four agents yielded significant changes in two of 20, seven of 18, four of 16, and 16 of 18 variables, respectively.

Similarly, on addition of nitrous oxide to enflurane, there was no other evidence of sympathetic stimulation, such as was seen with the other potent inhalational agents.[2-4] Thus, the pupils did not dilate, nor did esophageal or skin temperatures increase.

Finally, we saw no depth-dependent change. With halothane, fluroxene and ether, more prominent responses resulted at deeper levels of anesthesia,[2-4] as evidenced both by the greater number of variables responding and by a greater change in the variables that did respond.

What causes these differences in responses to the addition of nitrous oxide? Like other inhalational agents,[13] nitrous oxide can directly depress the circulation.[14,15] As with ether, cyclopropane, or fluroxene, the depressant effects of nitrous oxide may be partially or completely antagonized by sympathetic activation. The cause of this activation has not yet been determined. Nitrous oxide does seem more prone to produce it in the presence of other inhalational agents-[2-4] or by itself,‡‡ rather than in the presence of narcotics.[5-7] Even with halothane, a drug that produces less sympathetic activation than other agents, the sympathomimetic effect of nitrous oxide is significant.[2] The reason for a lack of response with enflurane is not clear. It cannot be due to an inhibition of sympathetic activation by enflurane, since the sympathetic response to elevated CO_2 during spontaneous§§ or controlled (Smith NT and Calverley RK, unpublished observations) ventilation is quite respectable during enflurane anesthesia. Furthermore, in the cat[16] sympathetic discharge increases when nitrous oxide is added to enflurane, although arterial pressure decreases markedly. Observations in the cat suggest that increased activity or even epileptiform discharges in the hypothalamic or limbic regions may be responsible for the increased sympathetic activity when nitrous oxide is added to a potent inhalational agent.[17]¶¶ Midcollicular or pretectal transsection attentuated or abolished the sympathetic response.[17,18]¶¶ Of interest is the

fact that the EEG and circulatory effects of adding nitrous oxide decreased in the following order: fluroxene, halothane, ether, enflurane, an observation that corroborates our human studies. Nitrous oxide added to enflurane produced almost no increased sympathetic activity, as in the present studies.

Studies of the past several years suggest that the circulatory effects of nitrous oxide are protean. They probably depend upon the species of animal,[2-4,16-22] type of ventilation (spontaneous *vs.* controlled,[2,7] prior duration of administration of the background agent, duration of administration of nitrous oxide before measurements are made, whether nitrous oxide is added or withdrawn,[2,23] whether the depth of anesthesia is changed,[3] the age and physical status of the patient,[24-27] the extent of surgical trauma or blood loss, the concentration of nitrous oxide, and the body temperature. Of these, one of the most important factors may be the background anesthetic. We have already outlined the differences among the potent inhalational agents. Nitrous oxide added to halothane does not depress, and may stimulate, the cardiovascular system in healthy subjects,[2,7]‡‡ in cardiac patients,[28] and in the dog.[19-21] On the other hand, nitrous oxide added to a narcotic–oxygen combination usually produces depression in man,[5,6] or in the dog,** with morphine[5,6] or with meperidine.**

Many of these factors can help to explain the differences between our results and those recently reported by Bennett *et al.*,[29] who observed progressive decreases in cardiac output, stroke volume, and arterial pressures as nitrous oxide was increased in 10-per cent increments from 10 to 60 per cent during enflurane anesthesia. This depression became significant at 20 per cent nitrous oxide. Numerous differences in protocol between our studies and theirs are apparent. The age of our subjects was half that of their patients. They used additional agents: meperidine, diazepam, atropine, thiopental, and pancuronium. Their data were recorded during surgical procedures. Body temperature probably decreased during their studies,[30] while it was maintained constant during ours. They set the concentration of enflurane to maintain a given range of arterial pressures, rather than to maintain a constant end-tidal concentration. Nitrous oxide was increased by steps, while we added the agent suddenly at its full concentration. We decreased the enflurane concentration to compensate for the second-gas effect of nitrous oxide, while they maintained inspired concentration constant. However, with their small increments, the second-gas effect of nitrous oxide probably had minimal impact. They determined cardiac output from the Warner pulse–contour method, whereas we used the dye-dilution technique. It is patently impossible, however, to establish the relative importances of these various fac-

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§§ Calverley RK, Smith NT, Eger EI, II, et al: Comparative cardiovascular effects of enflurane during spontaneous and controlled ventilation in man (abstr). Sixth World Congress of Anaesthesiology, 1976, p 74.

¶¶ Stockard JJ: Epileptogenicity of general anesthetics: Basic mechanisms and clinical significance. Thesis for Ph.D. in Neurosciences, University of California, San Diego, 1976.

tors in the differences between the results of our two studies.

COMPARISON OF EQUIPOTENT LEVELS OF ENFLURANE AND ENFLURANE–NITROUS OXIDE (GROUP II)

Adding nitrous oxide, of course, increases anesthetic depth. We therefore compared enflurane–oxygen with enflurane–nitrous oxide–oxygen at equivalent MAC levels. At equianesthetic levels, nitrous oxide–oxygen–enflurane is slightly less depressant than enflurane–oxygen. It is tempting to ascribe this difference to the simple fact that an equivalent amount of nitrous oxide is less depressing than enflurane. However, this does not explain our observation that nitrous oxide offers more of a protective effect at the deeper level: the greater the proportion of anesthesia provided by nitrous oxide, the greater should be its impact. Nor can the extent of epileptiform activity explain this phenomenon, since there is more activity with enflurane–oxygen than with enflurane–nitrous oxide–oxygen at equivalent depths.*** At any rate, the difference is small enough that the main consideration in choosing between the two mixtures should be the concentration of oxygen needed by the patient.

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