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Cardiovascular Responses to Nitrous Oxide during Enflurane and Oxygen Anesthesia

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For many years nitrous oxide was thought to have little influence on cardiovascular dynamics.[1,2] A number of recent reports[3–10] have demonstrated that, contrary to previous belief, nitrous oxide has significant cardiovascular effects, which may be depressant or stimulatory depending on the agent and concentration with which the gas is mixed, and possibly also a host of other factors. The influence of nitrous oxide on cardiovascular dynamics during enflurane and oxygen anesthesia and operation has not been determined. In this study we investigated the dose–response effects of nitrous oxide on cardiovascular dynamics during anesthesia and operation with constant 2–3 per cent inflow concentrations of enflurane in oxygen.

METHODS

Twenty patients (12 male and 8 female) with an average age of 50 ± 8 years (range 23 to 57 years) and mean weight of 169 ± 17 pounds, scheduled to undergo elective lower-extremity orthopedic or abdominal surgical operations, served as the experimental subjects. The study was approved by the Medical Center Human Study Committee. Informed, written consent was obtained from every patient at the preoperative visit.

No patient was receiving alpha- or beta-adrenergic receptor blockers or stimulators or diuretic medications preoperatively. Premedications included meperidine (50–75 mg), diazepam (5–10 mg) and atropine (0.4–0.5 mg) intramuscularly 90 minutes before the scheduled operation. Prior to anesthesia an intravenous infusion was started in an upper extremity, a central venous pressure catheter was placed percutaneously into the superior vena cava or right atrium from the cephalic vein in the antecubital fossa or internal jugular vein in the neck, and a radial or brachial artery catheter was inserted percutaneously and threaded 30–72 cm into the central aorta. The aortic pressure catheter was attached via an arterial pressure transducer to a computer module terminal in the operating room. Warner's method[11] of analyzing the central aortic pulse-pressure curve was used to determine cardiac output, stroke volume, arterial blood pressure, and peripheral arterial resistance.

All patients were allowed to breathe 100 per cent oxygen for 5 minutes. Anesthesia was then induced with thiopental, 4 mg/kg, and the patient was paralyzed with pancuronium bromide, 0.1 mg/kg. Tracheal intubation was performed with a disposable endotracheal tube. Respiration was controlled with a volume-limited respirator at volumes of 10–15 ml/kg and rates of 8–12/min in order to maintain Pa_{CO_2} measured in aortic blood every 15–30 minutes between 30 and 35 torr. Anesthesia was maintained with an inflow concentration of 2–3 per cent enflurane in oxygen issuing from a calibrated Ohio enflurane vaporizer so that systolic arterial blood pressure was kept between 110 and 140 torr. A semiclosed circle system provided CO_2 absorption and a total fresh gas inflow of 5–6 l/min. Continuous monitoring of the electrocardiogram and recording of arterial and central venous pressures were performed.

Data were obtained after a minimum equilibration period of 45 minutes following each change in enflurane concentration. Periods chosen for data collection included those during which there was minimal and consistent surgical stimulation. Recordings were made during ventilation with 97–98 per cent oxygen and after nitrous oxide (10, 20, 30, 40, 50 and then 60 per cent) had been progressively added to the inspired mixture. Enflurane inflow concentration was maintained constant during changes in nitrous oxide. After each change

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TABLE 1. Cardiovascular Effects of 10–60 Per Cent Nitrous Oxide during Enflurane and Oxygen Anesthesia (Means ± SD)

	Per Cent Nitrous Oxide						
	0	10	20	30	40	50	60
Cardiac output (l/min)	4.4 ± 0.5	4.2 ± 0.6	3.9* ± 0.4	3.6* ± 0.5	3.5† ± 0.6	3.3† ± 0.3	3.1† ± 0.3
Stroke volume (ml)	52 ± 6	46 ± 5	44* ± 5	40† ± 4	39† ± 6	36† ± 4	34† ± 4
Heart rate (beats/min)	92 ± 12	96 ± 9	94 ± 9	89 ± 8	89 ± 10	88 ± 8	88 ± 7
Peripheral vascular resistance (PRU)	184 ± 23	185 ± 14	188 ± 13	188 ± 17	196* ± 9	204† ± 16	226† ± 18
Blood pressure (mm Hg)							
Systolic arterial	124 ± 9	117 ± 8	115* ± 9	106† ± 7	104† ± 6	103† ± 9	102† ± 7
Diastolic arterial	72 ± 5	69 ± 6	66* ± 6	65* ± 4	64* ± 4	61† ± 5	60† ± 4
Mean arterial	92 ± 6	88 ± 6	86* ± 5	80† ± 5	79† ± 7	77† ± 5	77† ± 3
Central venous	10 ± 2	9 ± 2	10 ± 3	10 ± 2	8 ± 2	8 ± 2	8 ± 2

* $P < .05$, † $P < .025$, Student's t test for paired data.

in nitrous oxide concentration, a 15-minute period of equilibration was allowed before initiating measurements of heart rate, stroke volume, cardiac output, systemic vascular resistance, and systolic, diastolic, and mean arterial blood pressures. No other supplemental anesthetic agent was employed prior to or during periods of data collection.

RESULTS

The 20 patients received an average inflow concentration of enflurane of 2.6 ± 0.4 per cent during the study procedures. Addition of nitrous oxide resulted in dose-related decreases in cardiac output, stroke volume, and systolic, diastolic, and mean arterial blood pressures in all patients, which became significant, $P < .05$, at 20 per cent (table 1). Nitrous oxide did not alter heart rate or central venous pressure at any concentration, but produced dose-related increases in peripheral vascular resistance that were significant, $P < .05$, at 40 per cent. After 15 minutes of 60 per cent nitrous oxide, cardiac output was reduced an average of 30 per cent and systolic arterial blood pressure 18 per cent, while peripheral arterial resistance was increased 23 per cent compared with enflurane–oxygen controls.

DISCUSSION

Utilization of nitrous oxide as a supplement during anesthesia with other agents has produced evidence of cardiovascular stimulation as well as depression.[6–10] Hornbein *et al.*[6] found that adding 70 per cent nitrous oxide to the anesthetic mixture in healthy, spontaneously breathing volunteers anesthetized with a constant end-tidal concentration of 0.8 per cent halothane, increased arterial blood pressure, cardiac output, and heart rate, and tended to decrease peripheral arterial resistance; adding it to the inspired gas administered to the same subjects during equilibration to a constant end-tidal concentration of 1.5 per cent halothane reduced all of the above-mentioned variables. In a similar investigation in volunteers anesthetized with fluroxene and oxygen, Smith and co-workers[8] found that addition of 70 per cent nitrous oxide resulted in changes compatible with alpha-adrenergic stimulation at 5 per cent fluroxene (systemic vascular resistance and mean arterial pressure increased an averaged of 20 per cent), but at 9 per cent fluroxene, a mixed alpha- and beta-adrenergic stimulatory response was obtained (cardiac output increased a mean of 18 per cent, mean arterial pressure 25 per cent and heart rate 11 per cent). These investigators found no evidence of cardiovascular depression (*e.g.*, reduction in stroke volume, cardiac output, or blood pressure) when nitrous oxide was added to fluroxene. In contrast, addition of nitrous oxide during morphine (2 mg/kg) and oxygen anesthesia resulted in marked concentration-dependent decreases in cardiac output, stroke volume, and arterial blood pressure.[9]

All of the above-mentioned observations suggest that it is difficult to classify nitrous oxide as a cardiovascular stimulant or depressant. It appears that many variables, including: amount and type of premedication; the primary agent and its concentra-

tion; duration of anesthesia, conduct of respiration, *i.e.*, controlled or spontaneous ventilation; condition of the recipient, *i.e.*, young healthy volunteer versus sick patient during operation; method of controlling the concentration of the primary agent, *i.e.*, constant end-tidal versus constant inflow concentration; and possibly a host of other factors may influence and alter the response of the cardiovascular system to supplementation with nitrous oxide during anesthesia with another agent.

The present investigation was designed to mimic clinical usage of nitrous oxide as a supplement during enflurane and oxygen anesthesia and operation. Because of this, constant inflow concentrations of enflurane rather than constant end-tidal concentrations of the gas were employed during addition of nitrous oxide. Our results under these conditions demonstrate that addition of nitrous oxide during anesthesia with 2–3 per cent enflurane and oxygen in patients undergoing operation with controlled ventilation results in significant concentration-dependent reductions of stroke volume, cardiac output, and arterial blood pressure and an increase in peripheral vascular resistance. While plasma catecholamines were not measured, our data suggest that nitrous oxide does not result in significant sympathetic stimulation when added during anesthesia with these concentrations of enflurane and oxygen.

Although our findings do not demonstrate the mechanism of cardiovascular depression after addition of nitrous oxide, the absence of significant peripheral vascular effects with simultaneous reductions in stroke volume and cardiac output during administration of 20 and 30 per cent concentrations of the gas suggests a direct negative inotropic influence. Lappas *et al.*[10] have found that the depression of cardiovascular dynamics that occurs when nitrous oxide is added to large doses of morphine is due to isolated impairment of left ventricular function. The absence of change in central venous pressure coupled with decreases in arterial pressure and cardiac output during administration of nitrous oxide in this study is compatible with a similar mechanism of isolated left ventricular depression found by Lappas and co-workers.

Other explanations of increased cardiovascular depression after addition of nitrous oxide during constant inflow enflurane concentration could be an interaction of nitrous oxide and the meperidine premedication in the cardiovascular system, or the "second-gas effect" or "concentration effect" of nitrous oxide on alveolar enflurane concentration. Since neither inspired nor end-expired enflurane concentrations were measured, it is difficult to know exactly how important the "second-gas effect" or "concentration effect" of nitrous oxide was in this study.

Our data in this investigation should not be interpreted to suggest that nitrous oxide should be avoided during anesthesia with enflurane, or that enflurane–oxygen–nitrous oxide is more depressant at equal depths of anesthesia than enflurane–oxygen anesthesia. Indeed, a recent report by Smith *et al.*‡ has demonstrated just the opposite, that is, at equi-MAC levels, enflurane–nitrous oxide is less depressant to cardiovascular dynamics than enflurane–oxygen. Rather, our observations simply emphasize that nitrous oxide produces significant cardiovascular depressant effects when added as a supplement during anesthesia with a constant inflow concentration of 2–3 per cent enflurane and oxygen. Consequently, its employment under these conditions should be undertaken with appropriate caution.

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