Nitrous Oxide Attenuates Pressor but Augments Norepinephrine Response to Laryngoscopy and Endotracheal Intubation

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Nitrous oxide (N_2O) exerts a sympathomimetic action. We investigated whether N_2O modifies the cardiovascular responses to tracheal intubation during general anesthesia. One-hundred healthy patients were assigned randomly to receive one of four concentrations (0%, 25%, 50%, or 75%; $n = 25$ each) of N_2O in oxygen throughout the study beginning 3 min before tracheal intubation. Anesthesia was induced with IV thiopental (5–7 mg/kg) whereas patients were ventilated with designated concentrations of N_2O. Tracheal intubation was facilitated with IV vecuronium (0.12 mg/kg). After intubation, all received 2% sevoflurane in oxygen via a semiclosed anesthesia circuit. Systolic arterial blood pressure, heart rate and rhythm, and plasma catecholamine concentrations were measured. The intubation significantly increased arterial blood pressure and heart rate. The maximum pressure changes were 46 ± 21 and 65 ± 24 mm Hg in 75% N_2O and control groups, respectively ($P < 0.05$), being attenuated by N_2O without affecting the tachycardiac response. Norepinephrine concentrations were increased at 1 min after the intubation, the magnitude of which was augmented by N_2O. N_2O did not affect the incidence of arrhythmias. It was shown that N_2O suppressed the pressor response to endotracheal intubation, despite the augmented increase of norepinephrine concentrations.

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Laryngoscopy and endotracheal intubation are associated with tachycardia, hypertension, and arrhythmias (1) caused, in part, by a reflex sympathetic discharge (2–4). In patients undergoing coronary artery bypass graft surgery, the use of an anesthetic during the induction that has a sympathetic stimulating property is associated with a greater hemodynamic change (i.e., tachycardia and hypertension) and myocardial ischemia (5). Moreover, centrally acting drugs that increase sympathetic activity may increase anesthetic requirements and antagonize the effects of inhaled anesthetics on the brain (6). Nitrous oxide (N_2O) exerts a sympathomimetic action when used alone or in conjunction with other anesthetics (7,8). Therefore, an exaggerated cardiovascular response to tracheal intubation may be expected if N_2O is used during the induction of anesthesia.

Although transient hypertension and tachycardia are usually of little consequence, they may be hazardous, especially in patients with persistent hypertension, limited coronary or myocardial reserve, or cerebrovascular diseases (9). We determined the effects of N_2O on the cardiovascular responses to laryngoscopy and endotracheal intubation in healthy adult patients.

Materials and Methods

The study was approved by the Ethics Committee of the Chonnam National University Hospital. We studied 100 ASA physical status I patients aged 35–60 yr presenting for routine elective orthopedic, gynecological, or other general surgery under general anesthesia. Patients were excluded if any of the following applied: cardiovascular, pulmonary, or metabolic diseases, and patients older than 60 yr of age or younger than 35 yr. Patients who took medications that would influence autonomic or cardiovascular response to laryngoscopy and intubation were also excluded. After

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obtaining written and informed consent, all patients were premedicated with midazolam 0.1 mg/kg orally 60 min before the induction of anesthesia.

Before arrival in the operating room, all patients had an IV catheter placed to serve as a route for drug and fluid administration. Additionally, a 20-gauge catheter was placed into the radial artery to continuously monitor the blood pressure and to take blood samples. Heart rate (HR) was determined from electrocardiogram (ECG) traces. For each patient, a rest period of at least 30 min was allowed to elapse between the time of cannulation and the start of the study.

The patients were assigned randomly to receive one of four end-tidal concentrations ($n = 25$ for each) of N_2O throughout the study period: 0% (control), 25%, 50%, and 75%. Randomization was achieved using a table of random numbers. After breathing 100% oxygen, anesthesia was induced with thiopental 5–7 mg/kg IV, whereas patients were ventilated with the designated concentration of N_2O in oxygen through an anesthesia face mask connected to a semiclosed anesthesia circuit. Thiopental was injected at a steady rate of 10 mg/s until loss of consciousness, as assessed by loss of eyelash reflex. Vecuronium 0.12 mg/kg IV was used to facilitate endotracheal intubation. Three minutes after the induction, when neuromuscular block was achieved, intubation was performed within 15 s, and anesthesia was maintained using 2% sevoflurane (inspired) and designated concentrations of N_2O in oxygen. The fresh gas flow rate was adjusted to 6 L/min before and 4 L/min after the intubation. The lungs were mechanically ventilated using a ventilator to maintain an end-tidal carbon dioxide (CO_2) tension between 35 and 40 mm Hg. Routine monitoring included invasive measurement of systemic blood pressure, HR and rhythm by 5-lead ECG, and oxygen saturation by pulse oximetry. Throughout the experiment, the inspired and end-tidal concentrations of CO_2, sevoflurane, and N_2O were measured using a gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland), which was calibrated before each use. Data from patients in whom intubation required more than 15 s were excluded.

Arterial blood pressure (mm Hg) and HR (bpm) were recorded throughout the study. The baseline values were determined 1 min before the induction of anesthesia. Hypertension was defined as a systolic arterial blood pressure (SAP) more than 130% of the baseline value or >160 mm Hg, whereas hypotension was defined as SAP <70% of the baseline value or <90 mm Hg. Tachycardia and bradycardia were defined as a HR more rapid than 120 bpm and <60 bpm, respectively. A dysrhythmia was defined as any ventricular or supraventricular premature beat or any sustained rhythm other than sinus.

Arterial blood samples were drawn before the induction (baseline), 3 min after the induction with thiopental, and 1 and 5 min after the intubation. The samples were collected into prechilled tubes containing EDTA-Na and immediately centrifuged at 3000 rpm for 15 min at 4°C. The plasma was stored at −70°C until assayed for catecholamine concentrations. Plasma concentrations of norepinephrine and epinephrine were measured in duplicates using the technique of high-pressure liquid chromatography (10). The assay sensitivity was 10.0 pg/mL, and within-run precision coefficients of variation were 13.5% and 14.2% for norepinephrine and epinephrine, respectively.

All results are expressed as mean ± SD. Statistical analyses of the data were performed by two-way analysis of variance with repeated measures. A Scheffé test was used for multiple pair-wise comparisons when a significant difference was indicated with analysis of variance. Complication rates among the groups were analyzed using χ^2 test where appropriate. A P value <0.05 was considered statistically significant.

Results

Sex ratio, age, weight, height, and hemoglobin concentrations did not significantly differ among the groups (Table 1). Laryngoscopy and tracheal intubation began 3 min after the administration of thiopental. At this time, the end-tidal N_2O concentrations were 19% ± 2%, 33% ± 5%, and 55% ± 5% in the 25%, 50%, and 75% groups, respectively. The end-tidal concentration of sevoflurane 5 min after intubation was 1.5% ± 0.2%, which did not differ among the groups.

Table 2 shows SAP and HR before and after endotracheal intubation. Basal levels of SAP and HR were comparable among the groups. The induction of anesthesia with thiopental with or without N_2O significantly decreased SAP. The tracheal intubation then significantly increased SAP in all groups, which persisted into 2 min. N_2O significantly attenuated the magnitude of the pressor response and sped the restoration of blood pressure toward control level. The maximum increase of SAP in the 75% N_2O group was 46 ± 21 mm Hg, being significantly lower compared with that of 65 ± 24 mm Hg in the control group (Fig. 1). HR increased significantly after the induction of anesthesia and further increased after tracheal intubation, the degree of which did not differ among the groups (Fig. 1).

The incidence of hypertension was significantly less in the 50% N_2O and 75% N_2O groups compared with the control group. The incidence of hypotension, tachycardia, and bradycardia did not differ among the groups, nor did the incidence of ventricular ectopic beats differ among the groups. None developed ECG changes suggestive of myocardial ischemia during the anesthetic induction. The arrhythmias disappeared spontaneously without treatment (Table 3).

Table 4 shows the plasma catecholamine concentrations before and after endotracheal intubation. Basal concentrations of norepinephrine and epinephrine were not

Table 1. Demographic Data

	0% N_2O (n = 25)	25% N_2O (n = 25)	50% N_2O (n = 25)	75% N_2O (n = 25)
Sex (M/F)	13/12	7/18	9/16	9/16
Age (yr)	46 ± 9	47 ± 7	46 ± 8	46 ± 5
Weight (kg)	62 ± 15	63 ± 8	59 ± 7	63 ± 10
Height (cm)	163 ± 8	160 ± 7	160 ± 6	160 ± 8
Hemoglobin (g/dL)	12 ± 1	11 ± 1	12 ± 2	13 ± 1

Values are mean ± SD and n is number of patients. There were no statistically significant differences among the groups.

Table 2. Systolic Arterial Blood Pressure (SAP) and Heart Rate (HR) Before and After Endotracheal Intubation

	0% N_2O (n = 25)	25% N_2O (n = 25)	50% N_2O (n = 25)	75% N_2O (n = 25)
SAP (mm Hg)				
Baseline	132 ± 11	131 ± 11	133 ± 14	132 ± 12
Induction	116 ± 16*	118 ± 18*	115 ± 21*	110 ± 15*
Int-max	181 ± 26*	175 ± 22*	168 ± 26*	156 ± 26*†
Int-1	176 ± 27*	168 ± 26*	163 ± 27*	150 ± 26*†
Int-2	150 ± 28*	145 ± 27*	139 ± 22	131 ± 21†
Int-3	135 ± 26	130 ± 22	127 ± 16	120 ± 17†
Int-4	123 ± 25	117 ± 19*	113 ± 10*	108 ± 18*†
Int-5	116 ± 19*	108 ± 15*	105 ± 10*	101 ± 12*†
HR (bpm)				
Baseline	73 ± 13	73 ± 14	75 ± 12	69 ± 15
Induction	76 ± 11	79 ± 13	77 ± 13	73 ± 12*
Int-max	100 ± 13*	104 ± 16*	103 ± 12*	98 ± 13*
Int-1	97 ± 12*	98 ± 17*	98 ± 13*	93 ± 12*
Int-2	93 ± 10*	95 ± 15*	93 ± 13*	87 ± 13*
Int-3	90 ± 11*	91 ± 14*	89 ± 14*	85 ± 13*
Int-4	87 ± 11*	87 ± 14*	84 ± 15*	81 ± 13*
Int-5	84 ± 12*	85 ± 15*	81 ± 15	78 ± 12*

Values are mean ± SD and n is number of patients.
Induction = 3 min after administration of thiopental with or without N_2O; Int-max = maximum response within 1 min after intubation; Int-1, 2, 3, 4, and 5 = responses at 1, 2, 3, 4, and 5 min after intubation.
* $P < 0.05$ versus baseline; † $P < 0.05$ versus 0% N_2O group.

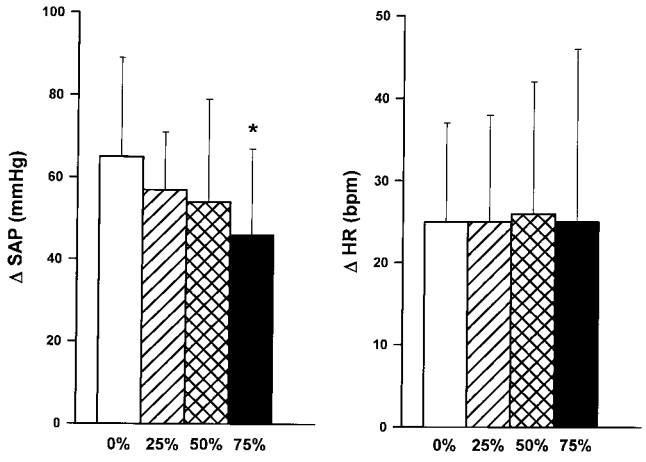

Figure 1. The maximum changes within 1 min after intubation from postinduction values in systolic arterial blood pressure (△ SAP) and heart rate (△ HR) in patients given nitrous oxide (0% = control, 25%, 50%, or 75%). Values are mean ± SD for 25 patients per each group. *$P < 0.05$ compared with 0% N_2O group.

different among the groups. The anesthetic induction with thiopental with or without N_2O similarly decreased the plasma concentrations of norepinephrine but not those of epinephrine. Tracheal intubation then increased norepinephrine concentrations when measured at 1 min after intubation, the degree of which was greater in the N_2O-treated groups than in control (Fig. 2). However, plasma epinephrine concentrations were increased significantly after intubation in the control group, which was then abolished by N_2O (Fig. 2).

Discussion

The most important finding of the present study is that N_2O attenuated the pressor response to tracheal intubation in adults. It is in line with previous observations in which N_2O and sevoflurane suppressed cardiovascular responses to tracheal intubation in children (11). It is also in agreement with the finding that N_2O, halothane, or enflurane attenuated the cardiovascular responses to intubation (12).

Table 3. Incidence of Adverse Effects

	0% N_2O (n = 25)	25% N_2O (n = 25)	50% N_2O (n = 25)	75% N_2O (n = 25)
Hypertension	21	18	13*	12*
Hypotension	3	4	3	2
Tachycardia (HR > 120 bpm)	2	4	3	1
Bradycardia (HR < 60 bpm)	0	2	1	1
Dysrhythmia	2	1	2	1

n = number of patients; HR = heart rate.
* $P < 0.05$ versus 0% N_2O group.

Table 4. Plasma Concentrations of Norepinephrine and Epinephrine

	0% N_2O (n = 25)	25% N_2O (n = 25)	50% N_2O (n = 25)	75% N_2O (n = 25)
Norepinephrine				
Baseline	200 ± 60	214 ± 71	209 ± 87	202 ± 50
Induction	179 ± 42*	177 ± 44*	174 ± 50*	162 ± 79*
PI-1	230 ± 80†	290 ± 107*†	287 ± 121*†	289 ± 121*†
PI-5	190 ± 81	210 ± 69	240 ± 101	245 ± 74
Epinephrine				
Baseline	47 ± 23	53 ± 23	57 ± 39	49 ± 25
Induction	45 ± 30	49 ± 29	54 ± 32	45 ± 36
PI-1	64 ± 30*†	53 ± 27	48 ± 31	40 ± 19‡
PI-5	50 ± 25	49 ± 27	41 ± 27	39 ± 20

Values are mean ± SD. Norepinephrine and epinephrine measured in pg/mL plasma.
n = number of patients; Induction = 3 min after administration of thiopental with or without N_2O; PI-1 and PI-5 = 1 and 5 min after the onset of intubation, respectively.
* $P < 0.05$ versus baseline; † $P < 0.05$ versus induction; ‡ $P < 0.05$ versus 0% N_2O group.

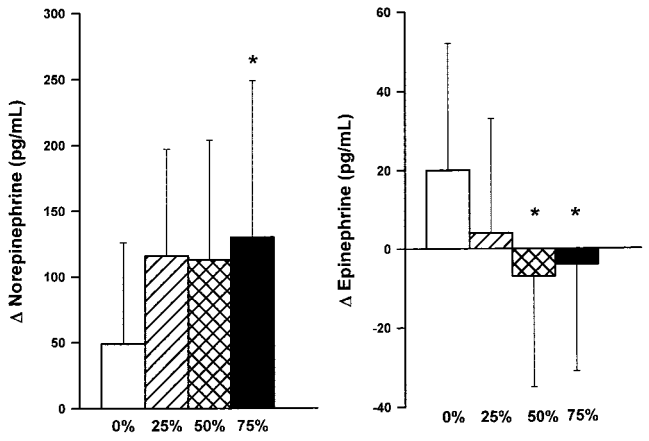

Figure 2. Changes at 1 min after intubation from postinduction values in plasma norepinephrine (△ norepinephrine) and epinephrine (△ epinephrine) concentrations in patients given nitrous oxide (0% = control, 25%, 50%, or 75%). Values are mean ± SD for 25 patients per each group. *$P < 0.05$ compared with 0% N_2O group.

The sympathomimetic effects of N_2O have been observed only when N_2O is used in the absence of any other noxious stimuli (7,8). It is thus likely that N_2O should attenuate the cardiovascular responses to any noxious stimuli, although it has mild sympathomimetic effects.

On the contrary, N_2O did not affect the tachycardiac response. This finding may be in line with a previous notion that deep inhaled anesthesia depresses the pressor response more effectively than the tachycardiac response (13,14). Moreover, a differential effect of an anesthetic on blood pressure and HR responses has been reported in which a small concentration of halothane (0.4%) attenuated the pressor but not the HR response, whereas a larger concentration (2%) attenuated both (12). Because the largest end-tidal concentration of N_2O (55%) was approximately 0.5 minimum alveolar anesthetic concentration in the present study, the failure of N_2O to modify HR may, in part, be attributed to its weak potency. In fact, minimum alveolar anesthetic concentration for endotracheal intubation is approximately 30% larger than that for surgical incision (15).

The endotracheal intubation increases SAP in proportion to plasma norepinephrine levels (3). In the present study, however, a correlation was lacking between norepinephrine concentrations and hemodynamic responses. In the control group, there was a larger increase in SAP despite a small increase of norepinephrine. Because succinylcholine has been associated with a greater release of catecholamines than nondepolarizing neuromuscular blocking drugs (3), the attenuated catecholamine response may be related

to the neuromuscular blocking drug used (i.e., vecuronium) in the present study.

In experimental groups, N_2O did not affect basal plasma norepinephrine concentrations before intubation. However, it augmented the norepinephrine response to intubation, whereas it diminished the pressor response. This finding is in line with that observed by Segawa et al. (16) in which isoflurane and sevoflurane suppressed hemodynamic responses to surgical noxious stimuli along with an augmented norepinephrine response. N_2O may not affect basal but augment already-stimulated sympathetic activity. However, the cardiovascular response to catecholamines may be attenuated by N_2O without affecting their secretion. As has been speculated earlier (16), the decreased blood pressure response may result from an attenuated cardiovascular response to catecholamines rather than from a suppressed sympathetic discharge.

On the contrary, the increased response of epinephrine to intubation was virtually abolished by N_2O. In previous studies, the plasma epinephrine concentrations were also increased in response to tracheal intubation (2,17). However, in these studies, the subjects were not premedicated with an opioid analgesic. If patients were premedicated with an opioid, no significant changes in epinephrine concentrations in response to intubation were demonstrated (18). Premedication with an opioid, even in small doses, may prevent the increase of epinephrine but not that of norepinephrine. Likewise, N_2O seems to prevent epinephrine but not norepinephrine response to endotracheal intubation.

Whether the sympathetic excitation because of N_2O is of clinical significance remains to be determined. In our study, no patients developed ECG changes suggestive of myocardial ischemia, and the incidence of premature ventricular contraction was similarly small among the groups. However, it has been observed that N_2O impaired the recovery of reperfused myocardium after an ischemic insult and increased mortality because of ventricular fibrillation in acutely instrumented dogs (19). Moreover, Houltz et al. (20) observed that N_2O, administered in the postbypass period in patients undergoing coronary artery surgery, induced regional wall motion abnormalities and alterations in the transmitral flow profile. The sympathetic stimulation may directly increase myocardial oxygen demand and adversely affect the coronary microcirculation (21). None of the subjects examined in the present study had documented coronary artery diseases. We may not exclude the possibility that N_2O may have a significant deleterious effect in high-risk patients with definite coronary artery diseases.

Limitations of our study may include a smaller end-tidal concentration of N_2O than the designated value. Three minutes may have been too short for an equilibrium to be reached. It would have been larger if the inflow gas was primed with N_2O or fresh gas flow was increased. Another limitation may be associated with an inadequate depth of anesthesia during endotracheal intubation. However, although the light anesthesia may enhance the hemodynamic response to intubation, the depth of anesthesia was about the same in all groups, so that it may have not influenced the results of our study.

In summary, the present study demonstrated that N_2O during general anesthesia attenuated the pressor response associated with laryngoscopy and endotracheal intubation, whereas it augmented the increases in plasma norepinephrine concentrations.

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