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Changes in hemodynamic variables and catecholamine levels after rapid increase in sevoflurane or isoflurane concentration with or without nitrous oxide under endotracheal intubation

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Abstract
Purpose. Rapid increases in concentrations of isoflurane and desflurane in oxygen have been shown to increase sympathetic activity. The aim of this study was to determine whether concomitant administration of nitrous oxide would reduce these sympathomimetic effects of volatile anesthetics.
Methods. Eighty healthy patients in whom the trachea was intubated and mechanically ventilated were given 15 min of anesthesia with either N_2O (67%)-O_2-sevoflurane (GOS), O_2-sevoflurane (OS), N_2O (67%)-O_2-isoflurane (GOI), or O_2-isoflurane (OI) (n = 20 per group). The inspired concentration of sevoflurane was 0.85% (0.5 minimum alveolar concentration [MAC]), and that of isoflurane was 0.6% (0.5 MAC). Fifteen minutes after endotracheal intubation, baseline and arterial blood sample data were obtained. Immediately after that, a sudden administration of 2.9 MAC volatile anesthetics was performed. Systolic and diastolic arterial pressures, heart rate, and end-tidal carbon dioxide concentration were obtained at 0.5, 1, 1.5, 2, 3, 4, and 5 min after that. To measure catecholamine levels, arterial blood samples were obtained 2 and 5 min after the trial started.
Results. Except for the OI group, systolic and diastolic arterial pressure progressively decreased after the abrupt increase in the concentration of volatile anesthetics. Except for the OS group, the heart rate increased after the abrupt increase in the concentration of volatile anesthetics. In the OI group, the end-tidal concentration of carbon dioxide increased at 0.5 and 1 min, suggesting that a slight hyperdynamic state occurred. However, it decreased progressively after the abrupt increase in volatile anesthetic concentration in the other groups. Plasma norepinephrine levels increased progressively in all groups.
Conclusion. Even if nitrous oxide was added to isoflurane or sevoflurane, the increase in heart rate could not be avoided. Contrary to previous reports, severe hyperdynamic circulation was not observed after a rapid increase in isoflurane concentration.

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Introduction

Rapid increases in the inspiratory concentration of isoflurane and desflurane in oxygen have been shown to induce hyperdynamic responses. [1–4]. A sudden increase in isoflurane concentration under endotracheal intubation is associated with a transient but clinically significant increase in heart rate, arterial pressures, and norepinephrine concentration [1]. The sudden administration of 5% isoflurane by mask caused immediate increases in blood pressure, heart rate, and rate pressure products in both normotensive and hypertensive patients [2]. A large, abrupt, stepwise increase in isoflurane and enflurane concentration administered via mask elicits tachycardia and hypertension, whereas sevoflurane and halothane do not induce hyperdynamic responses after increases in anesthetic concentration [3]. However, the effect of rapidly increased concentrations of volatile anesthetics combined with nitrous oxide on this activity has not been fully examined. Furthermore, our clinical impression is that, when a sudden increase in the concentration of isoflurane is given together with nitrous oxide under endotracheal intubation, there are no immediate transient increases in blood pressure and heart rate (hyperdynamic circulation). The aim of this study was to examine whether concomitant administration of nitrous oxide would reduce these sympathomimetic effects of volatile anesthetics.

Materials and methods

Patients

We studied 80 ASA 1–2 patients undergoing elective minor surgery. The Ethics Committee approved the

study, and each patient provided written informed consent. Patients who were receiving hypertensive or analgesic medication in the preoperative period or who had renal, hepatic, respiratory, neurological, or metabolic diseases were excluded.

Anesthesia

No premedication was given to the patients. In the operating room, a peripheral intravenous catheter was inserted into a cephalic vein. A radial artery was cannulated for continuous monitoring of arterial pressures (Custom Kit for Japan, Abbott Ireland, Sligo, Rep. of Ireland) and blood sampling. Continuous monitoring of the electrocardiogram lead II was initiated. Hemoglobin oxygen saturation (S_PO_2) was monitored by pulse oximetry.

We administered 5 mg·kg^{-1} of thiamylal for induction of general anesthesia and 0.2 mg·kg^{-1} of vecuronium to provide muscle relaxation for endotracheal intubation. After induction of anesthesia and tracheal intubation, patients were randomly assigned to one of four groups: N_2O (67%)-O_2-sevoflurane (GOS), O_2-sevoflurane (OS), N_2O (67%)-O_2-isoflurane (GOI), or O_2-isoflurane (OI) ($n = 20$ per group), and after tracheal intubation, the lungs were ventilated mechanically. In each group, the inspired concentrations of volatile anesthetics were maintained at 0.5 minimum alveolar concentration (MAC) for 15 min. We assumed MAC values for sevoflurane and isoflurane of 1.71% [5] and 1.15% [6], respectively. The patients' lungs were mechanically ventilated with a semi-closed circle system (Ohmeda Modulus CD Anesthesia System, Ohmeda, Madison, WI, USA) at a fresh gas flow of 6 l·min^{-1} (O_2, 6 l·min^{-1}; N_2O 4 l·min^{-1}-O_2 2 l·min^{-1}), and controlled ventilation was set at 8 breaths per minute, with a tidal volume of 8 ml·kg^{-1} and an inspiratory : expiratory ratio of 1 : 2.

Systolic and diastolic arterial pressures, heart rate, end-tidal carbon dioxide concentration ($P_{ET}CO_2$), SpO_2, and catecholamine levels were measured. The plasma concentrations of norepinephrine and epinephrine were measured in duplicate by high-performance liquid chromatography [7].

Fifteen minutes after endotracheal intubation, baseline measurements and arterial blood sampling were performed. The inspired concentration of isoflurane or sevoflurane was then increased rapidly to 2.9 MAC (sevoflurane 5.0%, isoflurane 3.3%) using a precalibrated vaporizer for sevoflurane (Sevotec 5, Ohmeda) or for isoflurane (Isotec 5, Ohmeda), and the measurements were repeated at 0.5, 1, 1.5, 2, 3, 4, and 5 min after the abrupt increase in the concentration of each volatile anesthetic. The study was completed before surgery started.

Measured values are expressed as means ± SD. Fisher's exact probability test was used to compare the sex ratio distributions among the four groups. Differences in age, weight, and height among the four groups were assessed by one-way analysis of variance (ANOVA). Intragroup comparisons of systolic and diastolic arterial pressures, heart rate, $P_{ET}CO_2$, norepinephrine, and epinephrine were performed by two-way ANOVA with repeated measures and paired *t* tests with Bonferroni's correction. Between-group comparisons were made at each time point by one-way ANOVA and unpaired *t* tests with Bonferroni's correction. A *P* value less than 0.05 was considered statistically significant.

Results

The patients' characteristics were not significantly different among the four groups (Table 1). Except for the OI group, systolic and diastolic arterial pressures decreased progressively after the abrupt increase in the concentration of volatile anesthetics (Fig. 1). The heart rate increased progressively 1.5 min after the abrupt increase in volatile anesthetic concentration in all groups except the OS group (Fig. 2). In the OI group, $P_{ET}CO_2$ increased at 0.5 and 1 min. However, it decreased progressively after the abrupt increase in volatile anesthetic concentration in the GOS, OS, and GOI groups (Table 2). Plasma norepinephrine levels increased progressively after the abrupt increase in volatile anesthetic concentration in all groups (Fig. 3). Plasma epinephrine levels increased progressively after the abrupt increase in volatile anesthetic concentration in all groups except the OS group (Fig. 4).

Table 1. Patient characteristics[a]

Group	*N*	Sex (M/F)	Age (yr)	Weight (kg)	Height (cm)
GOS	20	10/10	40.2 ± 14.7 (17–65)	61.3 ± 10.2 (40–80)	161.5 ± 7.0 (148.6–178)
OS	20	10/10	40.1 ± 9.9 (21–61)	60.4 ± 10.2 (41–75.6)	162.9 ± 7.7 (150.5–176.2)
GOI	20	10/10	41.3 ± 16.4 (17–64)	61.5 ± 10.2 (45–88)	164.4 ± 7.4 (153–178.5)
OI	20	10/10	39.1 ± 13.3 (19–63)	61.8 ± 15.1 (38.5–103)	162.5 ± 10.4 (145–179)

[a] Values are means ± SD (range). There were no significant differences among the groups studied. GOS group received N_2O (67%)-O_2-sevoflurane; OS group received O_2-sevoflurane; GOI group received N_2O (67%)-O_2-isoflurane; and OI group received O_2-isoflurane.

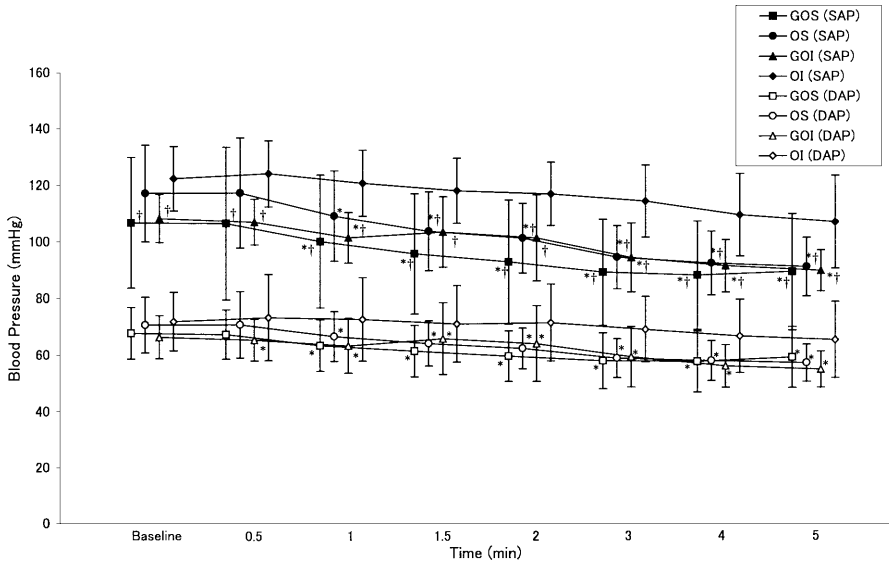

Fig. 1. Blood pressure. SAP, Systolic arterial pressure; DAP, diastolic arterial pressure; GOS, N_2O (67%)-O_2-sevoflurane; OS, O_2-sevoflurane; GOI, N_2O (67%)-O_2-isoflurane; OI, O_2-isoflurane. Values are means ± SD. *$P < 0.05$ compared with baseline. †$P < 0.05$ compared with the value for the OI group

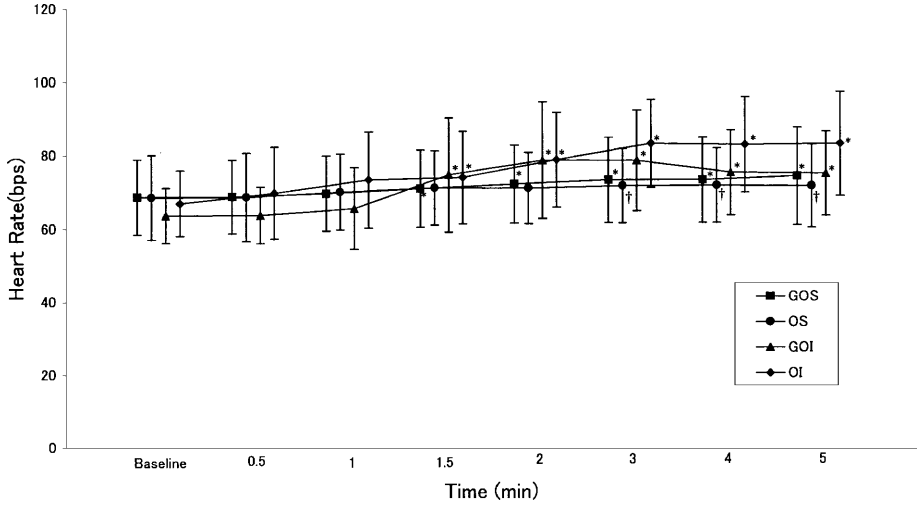

Fig. 2. Heart rate. Values are means ± SD. *$P < 0.05$ compared with baseline. †$P < 0.05$ compared with the value for the OI group

Table 2. End-tidal concentration of carbon dioxide ($P_{ET}CO_2$) (mm Hg) at various times[a]

	Baseline	0.5 min	1 min	1.5 min	2 min	3 min	4 min	5 min
GOS	31.1 ± 2.8	30.9 ± 2.8	30.6 ± 2.9	30.3 ± 3.0[b]	30.1 ± 3.1[b]	29.4 ± 2.8[b,c]	29.1 ± 2.8[b]	28.8 ± 2.9[b]
OS	31.9 ± 4.8	31.8 ± 5.0	31.9 ± 4.9	31.6 ± 4.8	31.3 ± 4.6[b]	30.6 ± 4.7[b]	30.3 ± 4.6[b]	30.1 ± 4.6[b]
GOI	32.6 ± 3.2	32.7 ± 3.1	32.8 ± 3.3	32.9 ± 3.2	32.6 ± 3.1	32.6 ± 3.1	32.1 ± 3.2[b]	31.8 ± 3.3[b]
OI	30.1 ± 2.4	30.7 ± 2.3[b]	30.7 ± 2.6[b]	30.6 ± 2.6	30.6 ± 2.5	30.5 ± 2.5	30.3 ± 2.7	30.2 ± 2.8

[a] Values are means ± SD.
[b] $P < 0.05$ *vs* baseline.
[c] $P < 0.05$ *vs* N_2O + isoflurane.
GOS group received N_2O (67%)-O_2-sevoflurane; OS group received O_2-sevoflurane; GOI group received N_2O (67%)-O_2-isoflurane; and OI group received O_2-isoflurane.

Discussion

Contrary to our expectations, even if nitrous oxide was added to isoflurane or sevoflurane, the increase in the heart rate could not be avoided. Doi and Ikeda [8] reported that sevoflurane was the least irritating anesthetic among halothane, enflurane, isoflurane, and sevoflurane. We believe that the reason tachycardia was found in the GOS group is not the pungency of sevoflurane, but rather the arterial baroreflex function

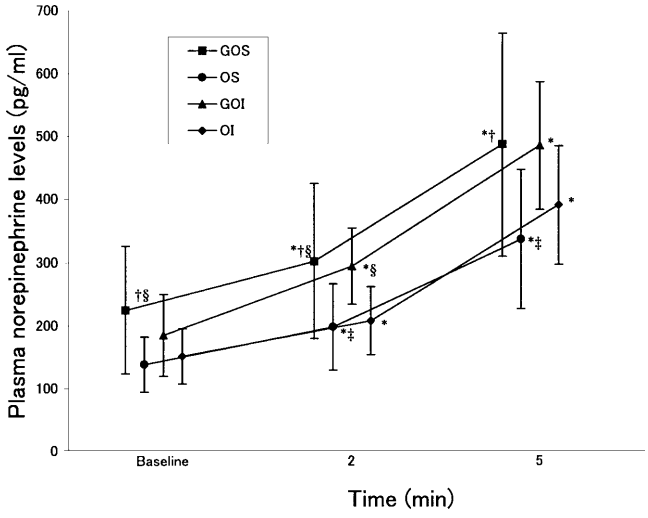

Fig. 3. Plasma norepinephrine. Values are means ± SD. * $P <$ 0.05 compared with baseline. † $P < 0.05$ compared with the value for the OS group. ‡ $P < 0.05$ compared with the value for the GOI group. § $P < 0.05$ compared with the value for the OI group

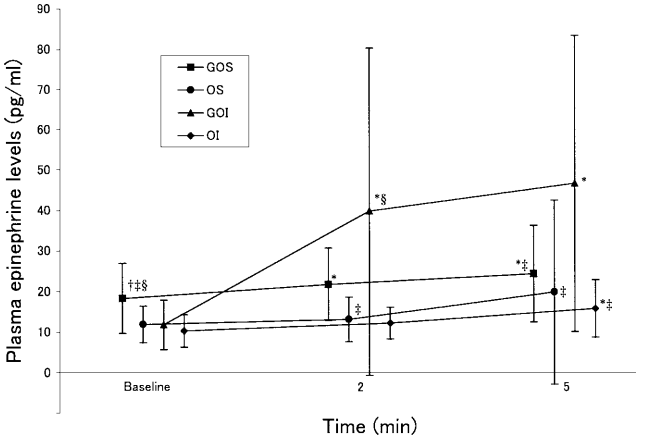

Fig. 4. Plasma epinephrine. Values are means ± SD. * $P <$ 0.05 compared with baseline. † $P < 0.05$ compared with the value for the OS group. ‡ $P < 0.05$ compared with the value for the GOI group. § $P < 0.05$ compared with the value for the OI group

[9]. Adachi reported that sevoflurane anesthesia induced reflex tachycardia when the patient's position was changed from the supine recumbent to the head-up tilt position, suggesting a possible maintenance of baroreflex control of the heart rate [10]. We believe that another factor that induced tachycardia in the GOI and OI groups was arterial baroreflex control of the heart rate. Kotrly et al. concluded that isoflurane anesthesia depresses baroreflex control of the heart rate in humans, but not to a substantially smaller degree than halothane or enflurane [11].

Furthermore, when the concentration of isoflurane was increased abruptly, severe hyperdynamic circulation did not occur in our study protocol (only the heart rate increased). Our results differed somewhat from those of Yli-Hankala et al. [1]. Their study showed that systolic arterial pressure increased significantly compared with baseline 2 min after an abrupt increase in isoflurane, and that diastolic arterial pressure increased significantly compared with baseline 1.5 and 2 min after that. In contrast, our study found that both systolic and diastolic arterial pressures remained constant throughout the time period in the OI group. We presume that the reason the results of the two studies differed is that Yli-Hankala et al. set up an initial end-tidal concentration of 1.3% isoflurane and suddenly increased the inspired concentration of isoflurane to 5%, whereas we abruptly increased the inspired concentration of isoflurane to 2.9 MAC (3.3%), which was lower than the concentration used by them. There are probably other reasons, such as the facts that the average age of our patients was about 10 years higher than that of the patients in their study, and that the number of patients used in our study was larger.

A sudden administration of 5% isoflurane by mask caused an immediate increase in the heart rate [2]. Tanaka et al. [3] increased the inspired concentration of sevoflurane or isoflurane by 0.9 MAC every 5 min to a maximum of 2.7 MAC via mask, and the heart rate did not change significantly throughout the time period in the sevoflurane group. However, it increased significantly from baseline during isoflurane administration at MAC levels of 1.8 and 2.7. Yli-Hanakala et al. [1] showed that the heart rate increased significantly compared with baseline from 1.5 to 10 min after an abrupt increase in isoflurane under endotracheal intubation. In the current study, the heart rate increased progressively in all groups except the OS group. We also believe that part of the reason why a rapid increase in the inspired concentration of isoflurane causes tachycardia is the irritating effect of isoflurane on the airways [1,2]. Ishikawa et al. [2] commented as follows: Because isoflurane is pungent, the heart rate responses are probably reflex responses. Although the site of stimulation was not defined in the study of Ishikawa et al., the nasal mucosa is the most likely site of stimulation, because the inhaled irritant reaches the nasal mucosa first, and the nasal mucosa is known to be particularly sensitive to chemical and mechanical irritation [12]. This is compatible with the observation that, in humans anesthetized via mask, nasal isoflurane insufflation elicits circulatory responses that can be halted by the nasal administration of lidocaine [13]. However, in this study, patients were under endotracheal intubation, and volatile anesthetics did not reach the nasal mucosa. Tomori and Widdicombe [14] suggested that the

epipharynx and nose are more sensitive than the lower respiratory tract in terms of the size of cardiovascular responses to mucosal irritation. Ishikawa et al. [2] also suggested that the possibility that the lower respiratory tract might be the site of stimulation cannot be excluded, and our results, which were obtained under tracheal intubation, support this suggestion.

$P_{ET}CO_2$ decreased progressively in the GOS, OS, and GOI groups but was sustained in the OI group (Table 2). There is a significant linear correlation between percent change in $P_{ET}CO_2$ and percent change in cardiac output [15,16]. We consider that the significant increase in $P_{ET}CO_2$ at 0.5 and 1 min compared with baseline shows a slight hyperdynamic state.

Plasma norepinephrine levels increased progressively in all groups (Fig. 3) because of the decrease in arterial blood pressure [17] and perhaps also because of the pungency of the volatile anesthetics, especially isoflurane. When N_2O was added to sevoflurane, plasma norepinephrine levels were higher throughout the time period (Fig. 3). This result is comparable to and compatible with reports that ventilation with nitrous oxide increased plasma norepinephrine [18]. Ventilation with nitrous oxide has been shown to augment sympathetic outflow [19,20], and nitrous oxide also attenuates the pulmonary uptake of catecholamine [21]. These may be the reasons for the increased concentration of norepinephrine during ventilation with nitrous oxide.

We obtained arterial blood samples to measure catecholamine levels 2 and 5 min after the trial began, because in the study of Yli-Hankala et al. [1] plasma norepinephrine levels increased significantly compared with baseline 1.5, 2, 4, 6, and 10 min after an abrupt increase in isoflurane.

In summary, we rapidly increased sevoflurane or isoflurane concentration with or without nitrous oxide in patients under endotracheal intubation and investigated hemodynamic variables and catecholamine levels. Contrary to our expectations, even if nitrous oxide was added to isoflurane or sevoflurane, the increase in the heart rate could not be avoided. Furthermore, when the concentration of isoflurane was increased abruptly, severe hypertension was not observed.

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