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Effects of Xenon on Hemodynamic Responses to Skin Incision in Humans

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Background: **The authors evaluated the hemodynamic suppressive effects of xenon in combination with sevoflurane at skin incision in patients undergoing surgery.**

Methods: **Forty patients were assigned randomly to receive one of the following four anesthetics: 1.3 minimum alveolar concentration (MAC) sevoflurane, 0.7 MAC xenon with 0.6 MAC sevoflurane, 1 MAC xenon with 0.3 MAC sevoflurane, or 0.7 MAC nitrous oxide with 0.6 MAC sevoflurane (n = 10 each group). Systolic blood pressure and heart rate were measured before anesthesia, before incision, and approximately 1 min after incision.**

Results: **The changes in hemodynamic variables in response to incision were less with sevoflurane in combination with xenon and nitrous oxide than with sevoflurane alone. Changes in heart rate (in beats/min) were 19 ± 11 (± SD) for sevoflurane alone, 11±6 for 0.7 MAC xenon–sevoflurane, 4 ± 4 for 1 MAC xenon–sevoflurane, and 8 ± 7 for nitrous oxide–sevoflurane. Changes in systolic blood pressure were 35 ± 18 mmHg for sevoflurane alone, 18 ± 8 mmHg for 0.7 MAC xenon–sevoflurane, 16 ± 7 mmHg for 1 MAC xenon–sevoflurane, and 14 ± 10 mmHg for nitrous oxide–sevoflurane.**

Conclusions: **Xenon and nitrous oxide in combination with sevoflurane can reduce hemodynamic responses to skin incision compared with sevoflurane alone. One probable explanation may be that xenon has analgesic properties similar to those of nitrous oxide, although the exact mechanism is yet to be determined. (Key words: Inhaled anesthetics; nitrous oxide; sevoflurane.)**

WITH continued concerns about the use of nitrous oxide (N_2O),[1–5] the interest in xenon anesthesia has increased. Xenon, a noble gas, possesses a clinically relevant anesthetic potency (minimum alveolar concentration [MAC] = 71%).[6,7] Its small blood–gas partition coefficient (0.115)[8] makes rapid induction and emergence possible.[9,10] Although its relatively high cost may limit clinical use, these properties, combined with the recent trend toward low-flow or closed-circuit anesthesia techniques, have caused anesthesiologists to reconsider using xenon.

The effects of surgical stimulation on the cardiovascular system during xenon anesthesia have been studied incompletely in humans. Several previous studies suggest that xenon causes minimal cardiovascular effects[11–13] and attenuates increases in plasma catecholamine associated with surgical stimulation.[11,12] However, medications such as pancuronium, fentanyl, or barbiturates were administered with xenon in these studies,[11–13] which may have affected the hemodynamic variables.[14,15] Furthermore, xenon was compared with N_2O at unequianesthetic concentrations (1 MAC xenon *vs.* 0.7 MAC N_2O), and the surgical stimulation was not controlled,[12,13] suggesting that the different level of anesthesia and stimuli might have confounded the results. Therefore, to evaluate rigorously the autonomic nervous system responses to surgical stimulation during xenon anesthesia, we conducted a randomized study by choosing equal MAC concentrations without any adjuvants.

Materials and Methods

After we received approval from the Institutional Human Studies Committee of Teikyo University, we obtained informed consent from 40 adult patients classified as American Society of Anesthesiologists physical status 1 or 2 and undergoing elective lower abdominal surgery. They were to have at least 5-cm skin incisions on the lower abdomen. Most of them were scheduled for either gynecologic or colorectal surgery. The patients scheduled for laparoscopic surgery were excluded because of its small skin incision. Other exclusion criteria were history of cardiac and pulmonary abnormalities, hypertension and use of medications that might affect blood pressure, heart rate (HR), and MAC values of inhaled

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anesthetics. Preanesthetic laboratory values were within normal limits.

No patient received any premedication. After the patients were in the operating room, monitoring by an electrocardiograph, a pulse oximeter, and a noninvasive blood pressure cuff was begun. Anesthesia was induced with single vital capacity inhalation of 5% sevoflurane,[16] and tracheal intubation was facilitated with 0.10 to 0.15 mg/kg vecuronium administered intravenously. Using a computer-generated random-number table, the patients were assigned to one of four groups receiving equal MAC (1.3 MAC) anesthetic treatment (n = 10 each per group): 1.3 MAC sevoflurane (sevoflurane group), 0.7 MAC xenon with 0.6 MAC sevoflurane (0.7 MAC xenon group), 1 MAC xenon with 0.3 MAC sevoflurane (1 MAC xenon group), and 0.7 MAC N_2O with 0.6 MAC sevoflurane (N_2O group). The MAC value of xenon was assumed to be 71% at age 43 yr.[7,17] The MAC values of sevoflurane, N_2O, and xenon were adjusted to the patient's age using Mapleson's formula.[17] For the sevoflurane and N_2O groups, the target end-tidal concentration was achieved by a fresh gas flow of 3 l/min. For the xenon groups, the residual sevoflurane administered during inhalation induction was adjusted to the target concentration (0.3 or 0.6 MAC) by high-flow oxygen (6 l/min) for at least 10 min. Then oxygen was discontinued and the upright ventilator bellows was deflated completely and refilled quickly with 100% xenon with sevoflurane. Xenon was started at 2 l/min. Two or 3 min later, when the end-tidal concentration reached 1 or 0.7 MAC, the xenon flow was reduced, oxygen was resumed, and the anesthesia system was closed. Respiratory gases were sampled at the Y connector, and inspired and expired sevoflurane, N_2O, and carbon dioxide concentrations were monitored continuously using an infrared gas monitor (Ultima SV, Datex, Helsinki, Finland), which was calibrated just before each anesthetic with a tank standard. The xenon concentration was monitored continuously using a AZ720 xenon monitor (Anzai Medical, Tokyo, Japan), which used the absorption of a characteristic radiogram for the measurement. It was calibrated before each case using an 80% xenon–20% oxygen mixture analyzed to ± 0.02% accuracy (Nihon-Sanso, Tokyo, Japan). The effective working range for this monitor was 1% to 100%, with an error ± 1% and a 90% response time less than 1 s. The lungs were ventilated mechanically to maintain the end-tidal carbon dioxide concentration between 30 and 35 mmHg. No patient received any drugs other than those stated.

For approximately 30 min after tracheal intubation, the patients were left unstimulated except for positioning, preparation, and draping. The inhaled anesthetic concentrations remained stable at the target end-tidal concentration for at least 20 min before surgical incision. Heart rate and systolic blood pressure (SBP) were measured using a cuff with an automatic oscillographic method (Listmini BP-8800; Colin, Aichi, Japan) at the right arm before anesthesia was induced, 1 min before incision, at incision, and in "continuous" mode for 10 min thereafter. The Listmini BP-8800 can measure HR and SBP every 15–30 s in the continuous mode. The hemodynamic data were recorded on paper and analyzed by a person who was blinded to the anesthetic agents used. The SBP and HR before induction were recorded as the baseline hemodynamic variables. The SBP and HR at 1 min before incision were recorded as the hemodynamic variables during anesthesia. The peak SBP, which usually occurred 30 to 120 s after incision, and HR at the time were recorded as the hemodynamic variables at skin incision. All patients received approximately 10 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution for the duration of this study. The procedures lasted approximately 45 min.

Statistical Analysis

Chi-squared analysis was applied to compare differences in gender and American Society of Anesthesiologists classification among the four groups. All the other numeric data were first analyzed with normal probability plots to evaluate the validity of the assumption that the populations are normally distributed. Because the normality assumption was not rejected in the demographic data and hemodynamic variables, they were analyzed using parametric tests. Demographic data were analyzed with one-way analysis of variance. Hemodynamic data were analyzed using one-way analysis of variance (between groups) and repeated-measures analysis of variance (within the group). Multiple comparisons of hemodynamic data were performed using Tukey's honestly significant difference test.[18,19] The data are reported as the mean ± SD. P values < 0.05 were considered significant.

Results

The four groups did not differ significantly with respect to gender, age, height, weight, American Society of Anesthesiologists classification, or hemodynamic vari-

Table 1. Demographic Data and Baseline Hemodynamic Variables

	Sevoflurane	0.7 MAC Xe	1 MAC Xe	N_2O
Age (yr)	45 ± 10 (26–59)	46 ± 11 (20–60)	44 ± 5 (33–52)	43 ± 9 (24–59)
Weight (kg)	53 ± 4	55 ± 6	57 ± 11	55 ± 6
Height (cm)	156 ± 5	155 ± 4	158 ± 6	155 ± 7
Gender (M/F)	1/9	1/9	0/10	2/8
ASA Classification (class 1/2)	7/3	7/3	8/2	9/1
HR (bpm)	75 ± 13	92 ± 22	78 ± 14	73 ± 10
SBP (mmHg)	136 ± 19	135 ± 17	141 ± 26	135 ± 23

Data are mean ± SD (range). No significant intergroup differences were detected.

Xe = xenon; N_2O = nitrous oxide; HR = heart rate; SBP = systolic blood pressure.

ables before the administration of inhaled anesthetics (table 1). No patient had an abnormal electrocardiogram or a pulse oximetry value less than 98% during the study period.

Changes in Heart Rate

In the 0.7 and 1 MAC xenon groups, HR decreased significantly after anesthesia and remained at that level even after skin incision (92 ± 22 beats/min at baseline, 70 ± 17 beats/min before incision, and 81 ± 15 beats/min after incision for 0.7 MAC xenon–sevoflurane; 78 ± 14 beats/min at baseline, 63 ± 10 beats/min before incision, and 67 ± 9 beats/min after incision for 1 MAC xenon–sevoflurane). Heart rate remained stable after anesthesia and increased significantly after incision in the sevoflurane group, whereas HR decreased significantly after anesthesia and returned to the baseline level after incision in the N_2O groups. The increases in HR at incision were significantly greater in the sevoflurane groups than in the 1 MAC xenon and N_2O groups (change in HR: 19 ± 11 beats/min for sevoflurane, 11 ± 6 beats/min for 0.7 MAC xenon, 4 ± 4 beats/min for 1 MAC xenon, and 8 ± 7 beats/min for N_2O [fig. 1]).

Changes in Systolic Blood Pressure

In all four groups, SBP decreased after anesthesia and returned to the baseline level after skin incision. The increases in SBP at incision were significantly greater in the sevoflurane group than in the other three groups (change in SBP: 35 ± 18 mmHg for sevoflurane, 18 ± 8 mmHg for 0.7 MAC xenon, 16 ± 7 mmHg for 1 MAC xenon, and 14 ± 10 mmHg for N_2O [fig. 1]).

Discussion

Several lines of recent evidence suggest that volatile anesthetics, such as isoflurane,[20] cannot suppress hemodynamic responses to noxious stimuli. Zbinden *et al.*[20] showed that isoflurane cannot suppress hemodynamic reactions to painful stimuli; a normal blood pressure after stimulation can be achieved only if the prestimulation blood pressure is depressed to levels that may be clinically unacceptable. In contrast, supplementation with analgesics such as fentanyl and N_2O enables these volatile anesthetics to attenuate hemodynamic responses.[21] These concepts have been confirmed and extended by our results, which showed that, although sevoflurane alone did not suppress SBP and HR changes at skin incision, a substitution of sevoflurane for N_2O, an established analgesic,[22–26] or xenon can decrease hemo-

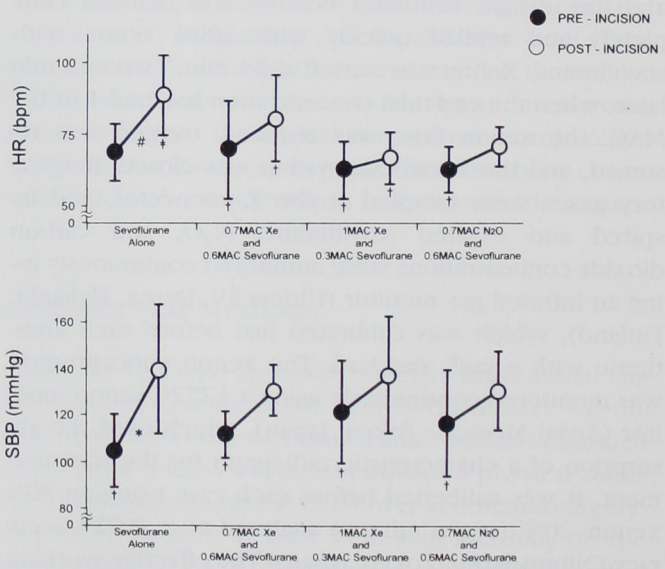

Fig. 1. Changes in heart rate (HR; *upper*) and systolic blood pressure (SBP; *lower*) from before to after incision. Data are expressed as the mean ± SD. †Significantly lower than the baseline within the group. ‡Significantly higher than the baseline within the group. #Increase in HR significantly higher than in the 1 MAC xenon and N_2O groups. *Increase in SBP significantly higher than the 0.7 MAC xenon, 1 MAC xenon, and N_2O groups.

dynamic changes. The opioid-like analgesic action of N_2O was shown by previous studies, which reveal cross-tolerance between N_2O and morphine[22] and partial reversal of N_2O-induced antinociception by naloxone.[22-34] Nitrous oxide increases the brain tissue concentrations of opioid peptides such as β-endorphine,[25] although it does not interact directly with opioid receptors.[26]

Furthermore, we have shown that xenon, similar to N_2O, reduces hemodynamic responses to skin incision. Because xenon causes minimal cardiovascular depression and preserves myocardial contractility,[11,12,27-29] this N_2O-like action of xenon can be attributed reasonably to its analgesic action. In fact, the analgesic properties of xenon have been suggested in humans and animals. Yagi *et al.*[30] reported a decreased incidence of pain during subanesthetic concentrations of xenon in human volunteers. Lachmann *et al.*[13] studied fentanyl requirements during 1 MAC xenon anesthesia and found that 80% of the patients required no fentanyl at skin incision to maintain their blood pressure within 20% of the baseline value. The mechanism of analgesic effects of xenon is described to be *via* suppression of spinal dorsal horn neurons[31] independent of α_2-adrenergic or opioid receptors[32] in experiments. These findings, in addition to our own, confirm the hypothesis that xenon possesses analgesic properties at clinically attainable concentrations in patients undergoing surgery.

Although the analgesic effect of xenon is likely to explain the similar hemodynamic response to incision between xenon and N_2O, it may not be the only explanation. For example, the other possible interpretation of the blunted responses in patients receiving xenon might be that xenon has some direct action at neuroeffector junctions, such as the vagal or sympathetic interface with the sinoatrial node or with the peripheral vasculature. Because these properties of xenon have not been studied, further investigation is necessary to identify the exact mechanism of the reduced responses to incision.

We administered xenon and sevoflurane with a closed-circuit technique to minimize the cost of xenon. Our use of a closed-circuit technique might be criticized on two grounds. First, the accumulation of foreign gases during the closed-circuit technique theoretically may have affected the infrared gas monitor, thus making the measurement inaccurate.[33] Second, sevoflurane may cause adverse renal effects at low flows because it is degraded by the strong bases in carbon dioxide absorbents to compound A, which is a nephrotoxin in rats.[34,35] However, the accumulation of foreign gases and compound A is expected to be minimal because of the short duration of closed-circuit anesthesia in our investigation (< 30 min). Denitrogenation by the initial high-flow anesthesia further reduced the accumulation of foreign gases. Furthermore, recent investigations suggest that low-flow sevoflurane anesthesia does not cause clinically relevant renal dysfunction.[36,37] Therefore, we do not believe that use of the closed-circuit technique put the patients at risk or compromised the accuracy of gas measurement.

It is impossible to administer more than 1 MAC xenon (71%)[7] to patients undergoing surgery because of potential hypoxic complications. We arbitrarily considered the surgically adequate and ethically acceptable level of anesthesia to be 1.3 MAC, which represents an approximately 95% effective dose for movement at skin incision with isoflurane.[38] The interaction between xenon and halothane in their effect on MAC has been shown to be additive.[7] Assuming the similar additivity between xenon and sevoflurane, 1 MAC xenon with 0.3 MAC sevoflurane and 0.7 MAC xenon or N_2O with 0.6 MAC sevoflurane are expected to represent 1.3 MAC. Therefore, we administered xenon with sevoflurane to ensure an adequate level of anesthesia, although we intended to evaluate the effects of surgical stimulation on the cardiovascular system during xenon anesthesia. Therefore, our results represent the combined effects of xenon and sevoflurane, rather than the effects of xenon alone, at skin incision. We do not believe that the use of vecuronium for neuromuscular blockade affected the results, because of the absence of cardiovascular effects of vecuronium.[15]

In conclusion, xenon and N_2O used with sevoflurane can reduce hemodynamic responses to skin incision compared with sevoflurane alone. One likely explanation may be that xenon possesses analgesic properties similar to N_2O, although the exact mechanism is yet to be determined.

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