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Subanesthetic sevoflurane does not affect sympathetic or parasympathetic function

KAZUYA KURAMOCHI

Department of Obstetrics and Gynecology, Musashino Red Cross Hospital, 1-26-1 Sakaiminamimachi, Musashino, Tokyo, 180 Japan

Abstract: To evaluate the effects of subanesthetic enflurane and sevoflurane on the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), the blood level of norepinephrine (NE) and fluctuations in the R-R intervals were measured on electrocardiogram in humans given either 0.5 MAC enflurane or sevoflurane. Enflurane suppressed circulating plasma NE and elevated coefficients of variation (CV) of R-R intervals after 20 and 30 min of inhalation. In contrast, 0.5 MAC of sevoflurane slightly stimulated cardiovascular function without any change in blood NE. Sevoflurane lowered the CV to 84% of control after 30 min of inhalation. These results indicate that subanesthetic concentrations of sevoflurane are unlikely to perturb sympathetic and parasympathetic activities in humans without surgical stimulation when compared with enflurane.

Key words: Sevoflurane, Sympathetic nervous system, Parasympathetic nervous system, Blood norepinephrine, R-R intervals

Introduction

The effects of inhalational anesthetics on the autonomic nervous system have been studied extensively. While diethyl ether, cyclopropane, and nitrous oxide have been reported to activate the sympathetic nervous system (SNS), halothane, methoxyflurane, enflurane, and isoflurane are claimed to suppress it [1–5]. Little information, however, has been available concerning the effects of inhalational anesthetics on parasympathetic nervous system (PNS) function.

Sevoflurane, a volatile anesthetic with a fluorocarbon skeleton, has recently been introduced into clinical use. There have been a few reports on the effects of sevoflurane on the autonomic nervous system, but they are not conclusive [6]. In the present study, the effects of subanesthetic sevoflurane and enflurane on SNS and PNS function were investigated.

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Patients and methods

Adult patients, 20–61 years of age, undergoing elective surgery were selected for the present study ($n = 8$). They were informed of the details of the study and their written consent was obtained. The subjects received no medication on the morning of the study, after having fasted overnight. They were brought to the operating room at 8 a.m. and venous and arterial catheters were introduced via the cubital vein and radial artery under local anesthesia. A cuff was attached to the other arm to measure arterial blood pressure. Three electrodes were attached on the chest to monitor a standard lead II electrocardiogram. Eight more electrodes were attached to the neck and thorax to measure cardiac output by an impedance method [7].

Blood pressure was determined every 2.5 min by the oscillometric technique (Type BS-2, Nippon Kolin, Japan). Electrocardiograms were displayed on a polygraph (Life Scope-8, Nihon Kohden Kogyo, Japan) and recorded as required. Cardiac output was measured using the impedance cardiograph (Cardiovascular Monitor Type NCCOM-3, Bomed). End-tidal carbon dioxide and inhalational anesthetic gas concentrations were determined using an analyzer (Anesthetic Gas Monitor Type-1304, Brüel-Kjær, Denmark). Minute volume was measured using a respirometer.

Study protocol

After preparation for the study and stabilization of the patient's mental condition, 0.5 MAC of sevoflurane (0.86%) or enflurane (0.84%) carried with 100% oxygen was administered to the patients using an anesthesia mask. The mask was tightly applied to the patient's face,

allowing no gas to leak. The airway was maintained by lifting the jaw manually, and spontaneous respiration was preserved after sedation or sleep. Inhalation of the anesthetic was continued for 30 min and measurements were made before and after 10, 20, and 30 min of inhalation. Ringer's lactate solution was infused at a rate of 5 $ml \cdot kg^{-1} h^{-1}$ during the study. The study was terminated when patients exhibited vigorous body movements, excitation, hypertension, hypotension, respiratory depression, and/or apnea, and effective treatment was provided.

Sevoflurane (Sevoflan) was purchased from Maruishi Pharmaceutical (Osaka, Japan) and enflurane (Ethrane) from Dinabott Pharmaceutical. The vaporizers were calibrated before use with an anesthetic gas analyzer. Concentrations of 1 MAC carried with 100% oxygen were determined to be 1.71% in the case of sevoflurane and 1.73% in the case of enflurane according to the brochures issued by the pharmaceutical companies.

Measurement of circulating plasma NE

The activity of the SNS was monitored by determining blood norepinephrine (NE) concentrations. Blood was collected before inhalation of the anesthetics, and after 10 min, 20 min, and 30 min of inhalation. Blood epinephrine (EN) and NE were analyzed by the high-performance liquid chromatography (HPLC) technique.

Monitoring of PNS activity

Changes in the R-R interval on the electrocardiogram were analyzed in accordance with the method described by Person and Solders [8], and Ewing et al. [9]. The electrocardiogram was fed into an automatic analyzer (Autonomic R-110, Fukuda Electronic, Japan). The analyzer summed the R-R intervals of 100 heart beats and displayed histograms of the intervals. It also calculated mathematical means and standard deviations (SDs) when the histograms showed normal distributions. Coefficients of variation (CV) between R-R intervals on electrocardiogram were obtained by dividing the standard deviations by the means. The CVs reflect the activity of the PNS.

Statistical analysis

Continuous variables were represented by mathematical means with SDs when distributions were normal. The null hypothesis was tested by one-way analysis of variance (ANOVA) and Student's *t*-test was used to test the difference between two groups when the null hypothesis was rejected. In the case of variables expressed as percent changes, the differences were analyzed by the signed-rank test. The statistical hypothesis was rejected when the risk was less than 5%.

Results

The study included eight patients in the sevoflurane group and five patients in the enflurane group. The background of the subjects in both groups is shown in Table 1. There were no differences in sex, age, or body weight distributions.

All patients who inhaled 0.5 MAC of either sevoflurane or enflurane became sedated within several minutes and went to sleep within 15–25 min. Depth of anesthesia according to the classification proposed by Guedel [10] indicated that the patients were in stage 3, plane 1 or 2.

Changes in systolic blood pressure, pulse rate, cardiac output, minute volume, CV, and blood EN and NE concentrations are shown in Table 2. There were no significant changes in systolic blood pressure or pulse rate in either group.

Percent changes in cardiac output compared with the preanesthetic control period are shown in Fig. 1a. Significant increases in cardiac output were observed after 10 min (116.8 ± 13.6% of control) and after 20 min (105.0 ± 15.4% of control) of inhalation in the sevoflurane group, but no changes were noted in the en-

Table 1. Changes in parameters during inhalation of enflurane for 30 min

	Control	10 min	20 min	30 min
Systolic BP (mmHg)	122 ± 15	128 ± 36	118 ± 28	115 ± 26
Heart rate (beat/min)	62 ± 12	68 ± 11	60 ± 14	60 ± 11
Cardiac output (l/min)	3.9 ± 0.8	3.6 ± 0.6	3.6 ± 0.8	3.4 ± 1.0
CV	4.6 ± 1.1	6.3 ± 2.9	4.1 ± 1.9	3.9 ± 2.3
Serum EN (pg/ml)	6.1 ± 4.5	2.8 ± 1.3	1.8 ± 1.1	1.5 ± 1.1
Serum NE (pg/ml)	31.8 ± 6.2	27.5 ± 8.7	24.0 ± 9.1	22.3 ± 8.3
Minute volume (l/min)	5.0 ± 1.5	5.1 ± 0.8	5.0 ± 1.2	4.9 ± 1.0
$EtCO_2$ (mmHg)	36.0 ± 4.7	33.6 ± 3.6	34.2 ± 4.3	34.6 ± 4.5

CV, coefficients of variation; BP, blood pressure; EN, epinephrine; NE, norepinephrine; $EtCO_2$, end-tidal CO_2.

Table 2. Changes in parameters during inhalation of sevoflurane for 30 min

	Control	10 min	20 min	30 min
Systolic BP (mmHg)	122 ± 15	125 ± 26	121 ± 23	118 ± 29
Heart rate (beat/min)	62 ± 12	65 ± 15	60 ± 19	61 ± 14
Cardiac output (l/min)	5.3 ± 0.9	6.1 ± 0.5	5.5 ± 0.7	5.0 ± 0.7
CV	4.6 ± 1.1	6.1 ± 0.7	4.1 ± 1.2	3.4 ± 0.8
Serum EN (pg/ml)	6.3 ± 2.0	3.5 ± 1.3	3.0 ± 1.2	2.4 ± 1.2
Serum NE (pg/ml)	20.1 ± 6.6	20.9 ± 6.0	18.5 ± 6.6	17.3 ± 7.9
Minute volume (l/min)	3.8 ± 0.86	5.0 ± 1.4	5.0 ± 1.3	4.6 ± 1.3
$EtCO_2$ (mmHg)	37.1 ± 2.9	32.9 ± 2.0	32.6 ± 3.2	33.5 ± 2.2

CV, coefficients of variation; BP, blood pressure; EN, epinephrine; NE, norepinephrine; $EtCO_2$, end-tidal CO_2.

flurane group. Figure 1b shows the percent changes in minute volume in both groups. While significant increases to 131.3 ± 21.2% at 10 min and 131.9 ± 16.3% at 20 min in the sevoflurane group were observed, no changes were observed in the enflurane group. There was no statistical difference on minute ventilation after 30 min of inhalation.

Blood concentrations of EN in both groups showed steady and significant decreases compared to preanesthetic controls after 10, 20, and 30 min of inhalation (Fig. 2a). No significant differences were observed between the two groups at any time during the study. Figure 2b shows the percent changes in blood NE. There was a significant reduction in NE in the enflurane group after 20 and 30 min of inhalation. No change was observed in the sevoflurane group.

The percent changes in CV shown in Fig. 2c revealed marked elevations in both groups after 10 min of inhalation. Significantly higher values than the preanesthetic

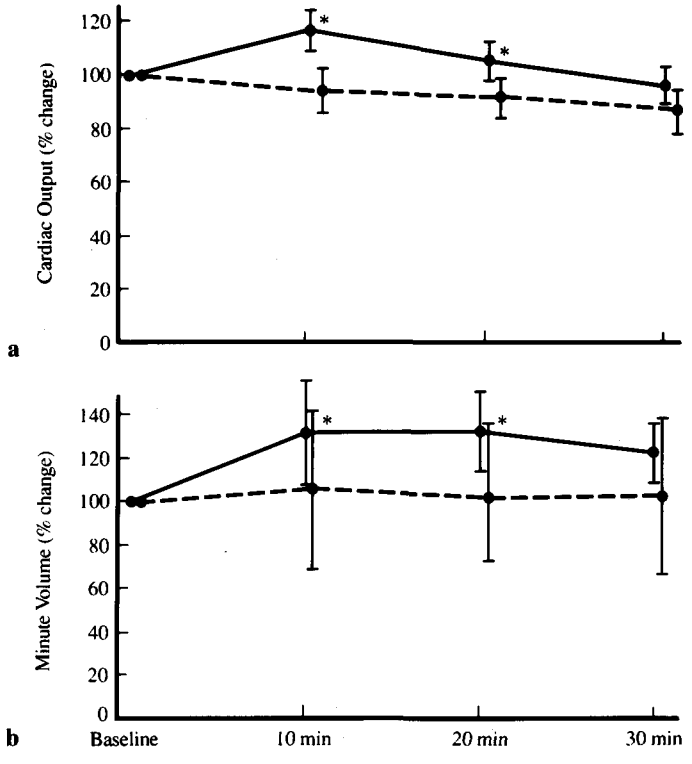

Fig. 1a,b. Effect of sevoflurane (solid line, $n = 8$) and enflurane (dotted line, $n = 5$) on **a** cardiac output and **b** minute volume. *$P < 0.05$

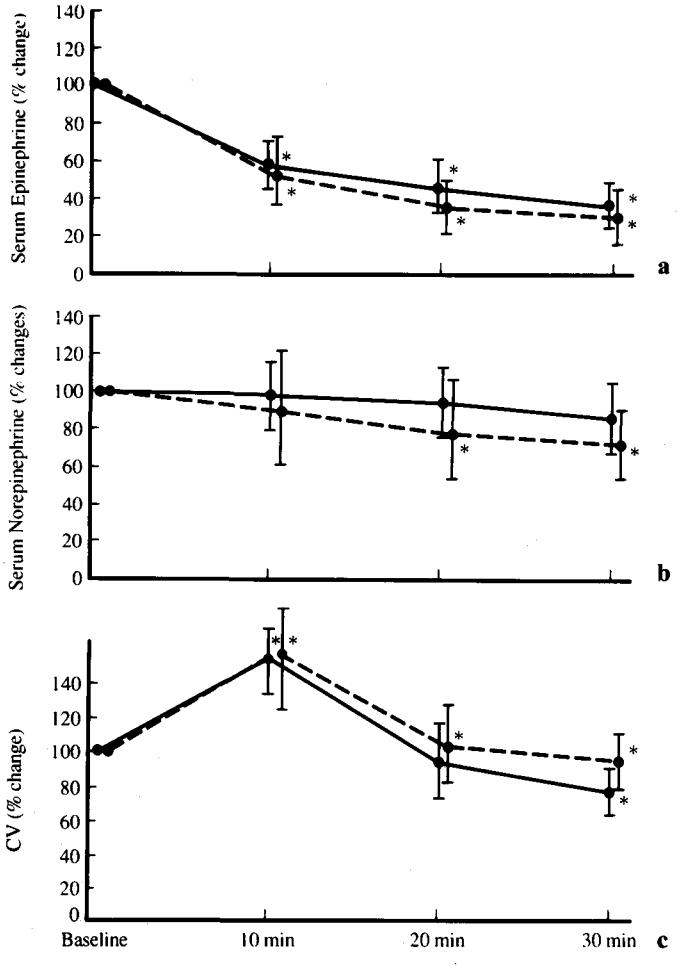

Fig. 2a–c. Effect of sevoflurane (solid line, $n = 8$) and enflurane (dotted line, $n = 5$) on **a** serum epinephrine, **b** serum norepinephrine, and **c** serum CV

control levels were observed in the enflurane groups after 20 and 30 min of inhalation. In contrast, a significantly lower value than the preanesthetic control was observed in the sevoflurane group after 30 min of inhalation. There was a clear difference between the two groups after 30 min of inhalation.

Discussion

In the present study, sympathetic and parasympathetic nervous system responses were investigated and compared in patients who received a subanesthetic concentration of sevoflurane and enflurane. A subanesthetic concentration of 0.5 MAC was used in the present study, since a preliminary study (unpublished data) revealed a rapid decrease in systolic blood pressure when the concentration exceeded 1.0 MAC. Such a rapid decrease in blood pressure would induce significant responses in neuroendocrine systems via sympathetic activation, including excessive release of catecholamines and corticosteroids.

Application of an anesthetic mask on patients' face for administration of inhaled anesthetic gas might cause some changes in the activity of neuroendocrine systems, but it did not induce any detectable release of NE into the bloodstream [11].

After 15–20 min of inhalation, some patients' eye movements ceased. Therefore, we judged the depth of anesthesia to be stage 3, plane 1 or 2 according to the classical Guedel classification. The author thought that the light stage of anesthesia was simulated in the present study.

The spontaneous respiratory cycles have been considered to be controlled by parasympathetic activities, and the higher minute volume or lower end-tidal CO_2 ($EtCO_2$) would be regarded as a relatively more potent stimulus of PNS activity. Based on the above mentioned factors, the CV value is considered to be a good indicator of the strength of the relative PNS activity.

There have been many reports on the effects of inhalational anesthetics on SNS activity, and researchers have taken several approaches to analyzing such activity.

In experimental studies, investigations have included monitoring the electrical activity of afferent nerves, the central nervous system, and the efferent nerves of sympathetic nerve tracts, measurements of blood pressure responses to electrical stimulation of nuclei in the medulla oblongata, and determination of blood catecholamines. Investigators [12–16] have reported a depression of the baroreflex, attenuation of action potentials from efferent nerves, and reductions in blood NE levels in animals given halothane, enflurane, and isoflurane, but potentiation of action potentials and elevation of blood NE levels were reported in animals exposed to diethyl ether, nitrous oxide, and cyclopropane.

In clinical studies, investigators have obtained action potentials from intrafascicular sympathetic nerves and/or determined the blood concentration of NE. Halothane, enflurane, and isoflurane attenuated the action potentials of peripheral sympathetic nerves and/or lowered blood NE levels [17–19]. Diethyl ether, cyclopropane, and nitrous oxide, on the other hand, stimulated such activity and/or elevated blood NE levels [20,21].

There has been only a limited number of papers describing the effects of sevoflurane on sympathetic nervous function. Murakawa et al. [6] observed no changes in blood EN or NE levels in patients inhaling sevoflurane in doses over 1 MAC. In contrast, we found that 0.5 MAC of sevoflurane lowered blood EN levels markedly. The differences can be explained as follows. Sevoflurane in doses over 1 MAC suppressed cardiovascular function and stimulated baroreflexes as mentioned above, activating the efferent outflow of sympathetic nerves to the adrenal glands, and the adrenal glands released EN, maintaining blood EN levels. Not only did subanesthetic concentrations of sevoflurane not attenuate hemodynamics, as shown by the higher blood pressure and cardiac output, and not increase outflow of sympathetic nerves to the adrenal glands, it even decreased EN levels in the present study.

While subanesthetic enflurane decreased blood NE levels after 20 and 30 min of inhalation, indicating depression of SNS function, subanesthetic sevoflurane did not lower blood NE concentrations. This finding led to the conclusion that the light stage of sevoflurane anesthesia may not suppress SNS function, whereas enflurane does.

There have been few studies on the effects of volatile anesthetics on the PNS, because investigators had no established methods of measuring its activity. In the 1970s Wheeler and Wilkins [22] discovered that fluctuations in the R-R intervals decreased markedly in patients with autonomic nervous system disorders due to severe diabetes mellitus, and suggested that the fluctuation was caused by an imbalance between SNS and PNS activity. Person and Solders [8] and Ewing et al. [9] demonstrated that fluctuations in the R-R interval reflect mainly PNS activity in the heart, and established that the CV of R-R intervals on the electrocardiogram can be used as an index of PNS activity. In a preliminary study, we observed a definite decrease in the CV for 25–90 min in patients who received 0.01 mg/kg of atropine sulfate.

The relationship between respiration and PNS has been studied, and spectral analysis of the R-R intervals revealed a marked correlation between respiratory fac-

tor and CV. The typical expression of altered PNS activity is respiratory sinus arrhythmia [23]. The results obtained in the present study were evaluated based on the assumption that PNS is deeply influenced by respiration.

Sevoflurane and enflurane in doses of 0.5 MAC markedly increased the CV after 10 min of inhalation, suggesting a predominance of parasympathetic nervous activity. Sevoflurane increased the minute volume and the CV value after 10 and 20 min of inhalation. Enflurane, on the other hand, showed consistently higher CV than sevoflurane. In both groups, the depth of anesthesia remained at stage 2, the stage of delirium, after 10 min of inhalation, since patients showed body movements, irregular respiration, and tachycardia.

In conclusion, 0.5 MAC enflurane depressed the SNS as shown by decreases in the blood levels of NE. PNS function appears to increase during inhalation of subanesthetic concentration of enflurane as reflected by increased CV values throughout the study. In contrast, 0.5 MAC sevoflurane stimulated the cardiovascular and respiratory system, maintaining SNS function as shown by the constant NE concentrations in the blood. Subanesthetic sevoflurane slightly lowered PNS function as shown by the attenuated CV after 30 min of inhalation.

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