NITRIC OXIDE SYNTHASE INHIBITOR SUPPRESS THE VASOCONSTRICTION DUE TO SEVOFLURANE IN CEREBRAL PIAL ARTERIES LARGER THAN 100 μm IN DIAMETER IN CATS

ASAO SYOHDA
Department of Anesthesiology,, Nara Medical University
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Abstract: **Background** Nitric oxide (NO) plays an important role in the reactivity of cerebral circulation to various stimuli. It is still unclear whether NO mediates the effect of sevoflurane on cerebral circulation. We therefore examined this question by measuring the diameter of pial arteries with or without exposure to NO synthase inhibitor, N ω-nitro-L-arginine methyl ester (L-NAME).

Methods The cranial window technique was employed in experiments using seven cats that received fentanyl and midazolam under mechanical ventilation. Diameters of cerebral pial arteries were observed through the cranial windows using an incident-light fluorescence microscope and video-recorded with a silicon-intensified target tube video camera system. Changes in arterial diameter were measured with an image analyzer after the experiments were finished. The diameters of pial arteries were measured under four conditions following the protocol below: 1) intravenous anesthesia; 2) intravenous plus sevoflurane anesthesia; then after L-NAME infusion, 3) intravenous anesthesia; and 4) intravenous plus sevoflurane anesthesia. Changes in vessel diameter were analyzed.

Results The arteries larger than 100 μm were significantly constricted ($p<0.05$) under sevoflurane inhalation; in contrast, after the administration of L-NAME, the arteries were not significantly affected by sevoflurane inhalation.

Conclusion L-NAME inhibited the vasoconstriction due to sevoflurane inhalation in cerebral pial arteries larger than 100 μm. In the cerebral pial arteries larger than 100 μm in diameter, NO synthesis was shown to be involved in vasoconstriction due to sevoflurane inhalation.

Index Terms

nitric oxide, nitric oxide synthase inhibitor, anesthetics, volatile, sevoflurane, vasoconstriction, pial arteries, cats

INTRODUCTION

The diameter of cerebral vascular vessels changes in response to various stimuli. The presence of a substance called endothelium dependent relaxing factor (EDRF) had been investigated since vasodilation is inhibited by injury to the vascular endothelium. In recent years, this factor has almost been identified as nitric oxide (NO)[1]. NO has attracted interest because it is not only a strong vasodilator but also plays various other roles. Especeally, involvement of NO in vascular reaction under various conditions has been investigated, and it is reported that NO largely affects cerebral circulation in the steady state or in response to

various stimuli and reactivity of cerebral vascular vessels to CO_2 or vasodilation by certain drugs[2-7].

Inhalation anesthetics reduce cerebral oxygen consumption, while in many cases, they possess cerebral vasodilating effects. Several studies on the inhalation anesthetic sevoflurane have been reported and species defferences have been observed in animal studies[8-11].

There also have been several reports on the role of NO in the effects of inhalation anesthetics on cerebral circulation[12-21].

In this study, the deameter of cerebral pial arteries during sevoflurane inhalation was measured before and after administrarion of NO synthase inhibitor N ω-nitro-L-arginine methyl ester (L-NAME) using the cranial window technique and the involvement of NO in the reactivity of cerebral circulation to sevoflurane was evaluated by differences in vascular diameters.

METHODS

This study was performed after approval of Animal Experimental Committee of Nara Medical University had been obtained.

Animals were allowed free access to food and water in the Institute of Laboratery Animals of Nara Medical University (room temperature: 23.4±0.6 ℃, humidity: 42.2±5.6 %) until they were anesthetized. Seven mongrel adult cats (2.4−4.2 kg) were administered 0.4 mg of pancuronium bromide (Nippon Organon Co. Ltd., Tokyo, Japan) after induction of anesthesia with ether (Wakoh Pure Chemical Industries Co. Ltd., Osaka, Japan) inhalation; then the trachea was intubated to control ventilation using an animal respirator (Harvard Respirator, Sumit Medical Co. Ltd., Tokyo, Japan). Anesthesia was maintained with a mixture of 33% oxygen and sevoflurane (Nippon Hoechst Marion Roussel Co. Ltd., Tokyo, Japan) in nitrogen until an intravenous route was secured. During mechanical ventilation, end-expiratory carbon dioxide pressure ($EtCO_2$) was continuously monitored using a CO_2 analyzer (HP 14360 A Carbon Dioxide Transducer, Hewlett Packard, MA, USA) to maintain pressure between 30 and 35 mmHg. After applying 1% lidocaine hydrochloride (Astra Japan Co. Ltd., Osaka, Japan) for local anesthesia, the femoral artery and vein were cannulated. The artery was used for continuous measurement of arterial blood pressure and blood sampling, while the vein was used for infusion and administration of drugs. After intravenous cannulation, anesthesia was maintained with 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of fentanyl (Sankyo Co. Ltd., Tokyo, Japan) 5 $mg \cdot kg^{-1} \cdot h^{-1}$ midazolam (Yamanouchi Pharmacetical Co. Ltd., Tokyo, Japan) and 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ of pancuronium bromide. Lactate Ringer solution was infused at 3 $ml \cdot kg^{-1} \cdot h^{-1}$.

Sevoflurane concentration was determined by an anesthetic gas concentration measuring apparatus (NORMAC®, ACOMA Co. Ltd., Tokyo, Japan). Arterial blood pH, $PaCO_2$, PaO_2, HCO_3 and hemoglobin were measured by a blood gas analyzer (ABL II®, Radiometer, Copenhagen, Denmark). Heart rate (HR), mean arterial pressure (MAP), and intracranial pressure (ICP) were continuously monitored during the experiment. Metabolic acidosis was corrected appropriately with sodium bicarbonate. Body temperature measured at the nasopharynx was maintained between 36.0 and 37.5 ℃ using a heating pad.

Preparation of cranial windows[22]

After fixing the head of the cat in an animal retainer, the cat was administered 1% lidocaine hydrochloride subcutaneously for local anesthesia, then the head was medially incised to expose the metopic to occipital cranial bones. A hole about 8 mm diameter was made in the circulation area of the middle cerebral arteries at each of left and right temporal regions of the head by using a drill and the dura and pia maters were removed. The holes were filled with artificial cerebrospinal fluid (Shimizu Siyaku Co. Ltd., Shimizu, Japan), covered with coverglasses and sealed with *a*-cyanoacrylate monomer (ALONALFA® , Toa Gousei Co. Ltd., Tokyo, Japan) to make an airtight seal. A vinyl chloride tube was inserted into one cranial window for continuous monitoring of ICP.

Preparation of fluorescein isothiocyanate-labeled red blood cells (FITC-RBC)[23]

Two milliliters of blood were obtained and red blood cells were separated by washing three times with physiological saline and centrifugation at 3,000 rpm for five minutes. The washed red blood cells were stirred for one hour in 10 ml of phosphate-buffered saline (pH 7.8) containing 1 $mg \cdot ml^{-1}$ of fluorescein isothiocyanate (FITC, Sigma Chemical Co. Ltd., St. Louis, MO) and FITC-labeled red blood cells (FITC-RBC) were obtained.

Measurement of diameters of cerebral blood vessels

Diameters of cerebral pial arteries were measured under a microscope connected to a video recording system. The cerebral pial arteries were distinguished from veins by FITC-RBC flow. After intravenous administration of FITC-RBC, the cerebral pial arteries were observed through one of the cranial windows using an incident-light fluorescence microscope (Nikon, Osaka, Japan) and video-recorded with a silicon-intensified target tube video camera system (SIT video ccamera system® , Hamamatsu Photonics, Hamamatsu, Japan). Changes in arterial diameter were measured with an image analyzer (ARGUS-10 ® , Hamamatsu Photonics, Hamamatsu, Japan) after the experiments were finished.

Time of measurement of cerebral vascular diameters

Cerebral vascular diameters were measured under four conditions following the protocol shown below:

1). under intravenous anesthetic administration (control).

2). 20 minutes after inhalation of sevoflurane under intravenous anesthetic administration.

Thirty minutes after discontinuation of sevoflurane inhalation and after the end-expiratory sevoflurane concentration decreased to 0.2 % or lower, 30 $mg \cdot kg^{-1}$ of L-NAME (Sigma Chemical Co., Ltd., Tokyo, Japan) dissolved in physiological saline was infused intravenously over 30 minutes, then:

3). under intravenous anesthetic administration.

4). 20 minutes after inhalation of sevoflurane under intravenous anesthetic administration.

Hemodynamic parameters, arterial blood gas analysis, and ICP were also measured at each time point.

Analysis of results

Vascular diameters (D) were classified by diameter under the control condition into the

following three group and degrees of change were compared:

1. D≦50 μm
2. 50 μm<D≦100 μm
3. 100 μm<D

Before and after administration of L-NAME, the change of vascular diameter was expressed as a percentage of difference between the diameter before (D iv) and during sevoflurane administration (D sevo) to that before sevoflurane administration by the following equation, and results were compared:

Percentage of vasular diameter change (%)=(D sevo-D iv)/D iv ×100(%)

Results were shown as mean ±standard error. For statistical analysis, two-way ANOVA with repeated measurements followed by Scheffe's F test were applied to hemodynamics, ICP, nasopharynx temperature, and arterial blood gas analysis. Wilcoxon matched-pairs test was applied to the percentage change of vascular diameter. A P value<0.05 was regarded as significant.

RESULTS

Hemodynamics, ICP and nasopharynx temperature are shown in Table 1. The ICP was increased significantly by sevoflurane inhalation and the mean blood pressure was significantly decreased by sevoflurane inhalation both before and after L-NAME administration. Other

Table 1. Hemodynamic Parameters, ICP, and BT without or with Sevoflurane Inhalation before and after Infusion of L-NAME

	before L-NAME		after L-NAME	
	I.V.	I.V.+Sevoflurane	I.V.	I.V.+Sevoflurane
HR (beats/min)	214±7	214±15	226±13	227±13
MAP (mmHg)	139±10	104±6*	167±12	126±8#
CVP (mmHg)	2±0.4	2±0.4	3±0.4	2±0.5
ICP (mmHg)	4.6±0.6	6.4±0.7*	5.8±0.6	6.7±1.0#
BT (℃)	36.6±0.4	36.9±0.4	37.0±0.4	37.1±0.4

All values are expressed as means±S.E.
HR=heart rates; MAP=mean arterial pressure; CVP=central venous pressure; ICP=intracranial pressure; BT=body temperature; I.V.=intravenous anesthesia
*=p<0.05 compared to I.V. values before L-NAME
#=p<0.05 compared to I.V. values after L-NAME

Table 2. Arterial Blood Gas Parameters without or with Sevoflurane Inhalation before and after Infusion of L-NAME

	before L-NAME		after L-NAME	
	I.V.	I.V.+Sevoflurane	I.V.	I.V.+Sevoflurane
pH	7.39±0.01	7.39±0.01	7.38±0.01	7.39±0.01
PaCO2 (mmHg)	33.4±1.5	32.4±1.2	32.9±1.2	31.6±1.1
PaO2 (mmHg)	152±6	136±2*	153±6	137±2#
HCO3- (mEq/L)	20.9±0.3	20.6±0.5	20.8±0.6	19.9±0.6

All values are expressed as means±S.E.
I.V.=intravenous anesthesia
*=p<0.05 compared to I.V. values before L-NAME
#=p<0.05 compared to I.V. values after L-NAME

Table 3. % Change in Diameter of Pial Arteries without or with Sevoflurane Inhalation before and after Infusion of L-NAME

Diameter of Pial Arteries (n)		before L-NAME		after L-NAME	
		I.V.	I.V.+Sevoflurane	I.V.	I.V.+Sevoflurane
D≦50	(62)	100	97.6±2.4	100	101.3±2.5
50<D≦100	(23)	100	97.5±1.9	100	99±2.9
100<D	(18)	100	92±2.4*	100	101±1.8

All values are expressed as means±S.E.
I.V.=intravenous anesthesia
*=$p<0.05$ compared to I.V. values before L-NAME

parameters were not changed by sevoflurane administration.

For arterial blood gas analysis (Table 2), PaO_2 decreased significantly both before and after L-NAME administration by sevoflurane inhalation. Other parameters were not changed significantly.

The measured vascular diameter ranged from 11 to 323 μm in the controls, and the specific details are shown in Table 3. In the cerebral pial blood vessels with a diameter of 50 μm or less and with a deameter larger than 50 μm and 100 μm or less, there was no change in the vessel size observed due to sevoflurane inhalation either before or after L-NAME administration. During sevoflurane administration before L-NAME administration, cerebral pial arteries constricted significantly to 92 % at 18 arterial sites with diameters between 100 and 323 μm, while there was no significant change observed due to sevoflurane inhalation after L-NAME administration.

The influence of L-NAME on the effect of the inhalation anesthetic sevoflurane on the diameter of cerebral pial blood vessels varied depending on the size of vessel diameter and larger vessels were affected more, I. e., the involvement of NO in the effect of sevoflurane on cerebral blood vessels was greater in larger vessels.

DISCUSSION

NO and NO synthesis inhibitor

NO is a known vasodilator that regulates the tone of cerebral blood vessels in the steady state. However, since the half-line of NO is very short, it is very difficult to confirm the presence of No directly or to investigate the biological response following administration of NO itself. Therefore, to investigate the role of NO in the body, NO synthase inhibitors are often used. For cerebral circulation, NO synthase inhibitors have been used to investigate the contribution of NO to the influence of hypoxia and vasopressors on cerebral ciculation. There also have been reports in which NO synthase inhibitors were utilized to study the role of NO in the influence of inhalation anesthetics on cerebral blood vessels or cerebral circulation[12-21]. In this study, using the cranial window technique in cats, cerebral blood vessels were observed to evaluate differences in NO involvement reflected by vessel diameter after L-NAME administration to determine the effect of sevoflurane on cerebral blood vessels. As a result, arteries with a diameter larger than 100 μm constricted significantly by sevoflurane inhalation and after L-NAME administration significant change in diameter was not observed by sevoflurane

inhalation.

Sevoflurane and cerebral circulation

In cats under anesthesia with midazolam and fentanyl, sevoflurane inhalation induced significant constriction of the cerebral pial blood vessels with a diameter larger than 100 μm. Several studies have reported the effects of inhalation anesthetics such as sevoflurane on cerebral circulation. In a study on the effect of sevoflurane anesthesia on cerebral circulation in patients with ischemic cerebral diseases, sevoflurane reduced cerebral blood flow and cerebral metabolism 34 % and 52 % respectively compared to conscious patients. In animal studies, cerebral oxygen consumption was decreased, while species difference was observed in the effects on cerebral blood flow[8-11].

Sevoflurane and NO

The possibility of endogenous NO involvement in the effect of inhalation anesthetics on cerebral circulation has been studied using NO synthase inhibitors. Changes in cerebral blood flow have been berified in some studies, while the role of NO in the effect of sevoflurane on cerebral blood vessels remains unclear. Further, it is unknown whether the response to sevoflurane differs depending on the size of blood vessels. In this study, the reactivity of cerebral pial blood vessels was examined before and after the administration of the NO synthase inhibitor L-NAME by cranial window technique to investigate the involvement of NO in the effect of sevoflurane on cerebral blood vessels. Inhalation of sevoflurane induced significant constriction of cerebral blood vessels larger than 100 μm and this constriction was clearly inhibited by the administration of NO synthase inhibitor. In arteries with a diameter of 100 μm or smaller, neither constriction induced by sevoflurane inhalation nor influence of NO synthase inhibitor was observed. From these results, NO synthesis was associated with constriction due to sevoflurane inhalation in blood vessels with a diameter larger than 100 μm, i. e., the blood vessels larger than 100 μm in diameter may have been constricted by a mechanism involving NO during the inhalation of sevoflurane.

It has been reported that inhalation anesthetics inhibit the effect of NO in excised blood vessels[17,20,21] and that endothelium-dependent vasodilation was reversed by sevoflurane inhalation in vivo study[18,19]. Also in the results of this study, in cerebral pial blood vessels larger than 100 μm in diameter, NO regulated the tone of blood vessels only during the first measurement under intraveous anesthesia before L-NAME administration, and at the second measurement under sevoflurane inhalation, vasodilation by NO was inhibited, inducing constriction of the vessels to 92 %. However, by L-NAME administration, NO synthesis was inhibited so that NO was not involved in the regulation of cerebral blood vessels, therefore cerebral pial arteries did not show any significant change due to sevoflurane inhalation on the third and fourth measurements. That is, after L-NAME administration, NO did not affect the regulation of blood vessel tone, thus the inhibitory effect of sevoflurane on NO was not exhibited. In contrast, in small arteries with a diameter of 100 μm or less, since NO synthesis and release which primarily induces vasodilation was not very involved in the regulation of the blood vessel tone, the influence of NO synthesis inhibition by L-NAME on the response of cerebral blood vessels to sevoflurane may not have been observed.

The mechanism was speculated to be as follows. The reactivity of cerebral vessels varies depending on the diameter of vessels, i. e., change in the diameter of large vessels differed from that of small vessels. Gotoh, *et al*[25]. proposed the "dual control hypothesis" for regulation of cereblral blood vessels. According to this hypothesis, large vessels with a diameter larger than 50 μm are sufficiently innervated so that the change in vessel diameter is mainly regulated neurologically. For typical instance, cerebral blood vessels have an autoregulatory reaction to blood pressure. However, in blood vessels with a diameter of 50 μm or less, innervation is sparse and the change in vessel diameter is mainly affected directly by chemical stimuli, local metabolism and blood gas partial pressure including CO_2. NO is known to regulate vessel tone during the steady state, and in that condition, a greater volume of NO is produced in large vessels than in small vessels. Farasi, et al.[26] reported that baseline synthesis of NO is greater in large vessels (275±10 μm) than in small vessels (62±6 μm), i. e., in large blood vessels, NO is more likely to be involved largely in blood vessel regulation. According to these hypotheses, the baseline level of NO synthesis and release is greater in large blood vessels, which implies that NO might regulate the baseline tone of blood vessels controlled by innervation. So, the influence of sevoflurane inhalation has been observed in pial arteries only with a diameter larger than 100 μm.

CONCLUSION

1. Sevoflurane inhalation induced marked constriction of cerebral pial arteries with a diameter larger than 100 μm. And this constriction by sevoflurane inhalation was clearly reversed by NO synthase inhibitor, L-NAME.
2. In the cerebral pial blood vessels with a diameter of 100 μm or less, there was no change in the vessel size observed due to sevoflurane inhalation either before or after L-NAME administration.
3. In the cerebral pial blood vessels larger than 100 μm in diameter, NO synthesis was shown to be involved in vasoconstriction due to sevoflurane inhalation.

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