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Differential vascular reactivity of canine mesenteric arteries and veins to sevoflurane

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Abstract

Purpose. The aim of this study was to compare the vascular reactivities of canine mesenteric arteries and veins to sevoflurane and to elucidate the underlying mechanism that is responsible for sevoflurane-induced hypotension.

Methods. Vascular rings of canine mesenteric arteries and veins were suspended in organ baths, and the effect of 2.3% and 4.6% sevoflurane on the contractile responses to transmural electrical stimulation (ES) and to norepinephrine (NE) were determined by recording isometric tension changes. The rings were contracted to a stable tension by the addition of NE and then exposed to increasing concentrations of sevoflurane (0%–5.1%).

Results. Sevoflurane attenuated the contractile responses to transmural ES in veins but not in arteries. The concentration responses to NE were not affected by sevoflurane in arteries or in veins. At stable precontraction induced by NE, when sevoflurane was placed in the bathing medium, arteries with intact endothelium had significant contraction at 1.7% and 3.4% sevoflurane, followed by relaxation at 5.1%. On the contrary, sevoflurane produced dose-dependent relaxation in endothelium-denuded arteries and endothelium-intact veins.

Conclusion. It is suggested that the relaxation of the veins by sevoflurane may be due to the inhibition of NE release from sympathetic nerve endings and to the direct inhibition of the contractile mechanisms of vascular smooth muscle. In arteries, sevoflurane causes endothelium-dependent vasocontraction, probably by inhibiting the release of basal endothelium-derived relaxing factor (EDRF).

Key words: Anesthetics, Volatile, Sevoflurane, Arteries, Mesenteric, Endothelium, Endothelium-derived relaxing factor, Pharmacology, Norepinephrine, Vein, Mesenteric

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Introduction

Sevoflurane is an anesthetic with a low blood-gas partition coefficient, which provides a rapid induction of anesthesia [1–3]. Like the other halogenated volatile anesthetics, sevoflurane induces a dose-dependent decrease in arterial blood pressure and cardiac output [3–5].

Nakamura et al. [6] recently showed that sevoflurane (1.7%–5.1%) induced a dose-dependent relaxation of canine coronary arteries precontracted with KCl. However, it is still unknown whether the vasodilating effects of sevoflurane depend on its ability to alter the sensitivity of vascular smooth muscle or its responsiveness to norepinephrine (NE). It has been demonstrated that halothane [7], enflurane [8], and isoflurane [9] attenuate the venous contractile responses to exogenously added NE as well as to endogenous NE [8,10,11]. However, to the best of our knowledge, it has not been reported in the literature whether sevoflurane inhibits the contraction induced by NE from ganglionic sympathetic nerve endings and by exogenously added NE.

The role of the endothelium in the vascular response to volatile anesthetics cannot be neglected, since endothelial cells control and modulate vascular relaxation through the release of endothelium-derived relaxing factor (EDRF) [12,13], which is now considered to be identical to nitric oxide (NO) produced from L-arginine by NO synthase in endothelium [14]. EDRF-induced relaxation is associated with increased levels of 3′,5′-cyclic guanosine monophosphate (cGMP) in smooth muscle, resulting from activation of soluble guanylate cyclase [15,16]. Several in vitro studies have demonstrated that halothane [17–21], enflurane [18,21], and isoflurane [18,21,22] induce endothelium-dependent changes in tension in isolated arteries by affecting the synthesis, release, transport, or activation of EDRF and/or the subsequent level of cGMP. Our laboratory

has provided evidence that sevoflurane impairs endothelium-dependent vasodilation in canine mesenteric arteries by an oxygen free-radical mechanism, mainly due to inactivation of EDRF [23]. This action of sevoflurane, on the contrary, causes vasocontraction in arteries, which may modulate vascular tone against excessive hypotension.

This study was undertaken to compare the vascular reactivities of canine mesenteric arteries and veins to sevoflurane and to elucidate the underlying mechanism of decreased arterial blood pressure observed during sevoflurane anesthesia.

Materials and methods

Preparation of vessels and isometric tension recordings

In accordance with the procedures required by our institutional animal care committee, superior mesenteric arteries and veins were taken from adult mongrel dogs of either sex (7–15 kg) after exsanguination during anesthesia with sodium pentobarbital (30 mg·kg,$^{-1}$, intravenously). The vessels were placed in cold modified Krebs-Ringer solution of the following composition (millimolar): 0.05 indomethacin to prevent volatile anesthetic-induced release of a vasodilating prostanoid from endothelium [18,24], 128.0 NaCl, 4.9 KCl, 1.2 $MgCl_2$, 1.6 $CaCl_2$, 14.8 $NaHCO_3$, 1.18 NaH_2PO_4, 10.0 dextrose, and 0.026 calcium disodium ethylenediaminetetraacetic acid (pH 7.4). The adhering fat and connective tissue were dissected off the blood vessels, which were cut into rings (2–3 mm in length, 1–3 mm internal diameter). The endothelium was mechanically removed in some artery preparations by careful abrasion of the intimal surface with filter paper. Endothelial integrity or denudation of the arteries was functionally confirmed by testing acetylcholine (10^{-6} M)-induced relaxation after a stable response to norepinephrine (3×10^{-6} M)-induced contraction.

The rings were suspended in a 20-ml water-jacketed tissue bath (37°C) and equilibrated for 120 min in solution continuously aerated with 95% O_2–5% CO_2. The solution was changed at 15-min intervals during equilibration. During this time, the artery and vein rings were stretched to a final tension of 2.0 and 1.5 g, respectively [8]. Tension development was measured with an isometric force transducer (Nihon Kohden, TB-612-T, Tokyo, Japan) and recorded using an amplifier (Nihon Kohden, AP-601-G) attached to a recorder (Nihon Kohden, PJ-691-G).

Some of the tissue preparations were placed between a pair of rectangular platinum electrodes (8 × 8 mm; 0.5 mm thick). The gap between the preparation and the electrode was wide enough to allow undisturbed contractions, and yet sufficiently narrow to permit effective stimulation of intramural nerve terminals. The rings were stimulated transmurally by a train of 2-ms square pulses of supermaximum intensity at frequencies of 1, 2, 4, 8, 16, or 32 Hz, at an amplitude of 9V, provided by a direct-current power supply and a switching transistor triggered by a stimulator (Nihon Kohden, SEN-3201). The responses of the vessel preparations to transmural electrical stimulation were measured for a long enough time to assure equilibrium responses.

Next, the effect of sevoflurane (2.3% and 4.6%) on the concentration-response curve was determined by the method of stepwise cumulative addition of norepinephrine (10^{-7}–10^{-3} M). To study the direct effects of sevoflurane on smooth muscle contraction and relaxation, the rings were first contracted to a stable plateau tension by the addition of NE at concentrations that elicited approximately 50% of the maximum contraction. They were then exposed to sevoflurane (1.7%, 3.4%, and 5.1%) until the tension had been stabilized.

Sevoflurane delivery

Sevoflurane was delivered from a vaporizer (Ohmeda, Sevotec 3, Steeton, England) in the O_2-CO_2 mixture aerating the bathing medium. The gas was humidified before entering the four serial tissue baths. The concentration in the resulting gas mixture was monitored continuously by an anesthetic gas monitor (WTI, AG101, Amsterdam, Netherlands) calibrated daily with a sevoflurane mixture. It was found that equilibration of the bathing medium with sevoflurane was complete within 30 min and that stable bath concentrations were achieved at a flow rate of the sevoflurane-O_2-CO_2 mixture of 300 ml·min^{-1} of gas flow through the fritted glass disks at the bottom of the four serial bath chambers, as previously described [23].

Drugs

The following drugs were used: sevoflurane (Maruishi Pharmaceutical, Osaka, Japan), DL-norepinephrine hydrochloride (Sigma, St. Louis, MO, USA), acetylcholine chloride (Sigma), and indomethacin (Sigma). All of these drugs except sevoflurane and indomethacin were dissolved in distilled water and diluted in the Krebs-Ringer solution gassed with a mixture of 95% O_2–5% CO_2 before being added to the tissue bath. Indomethacin stock solution was prepared by dissolving three parts indomethacin and one part sodium bicarbonate in distilled water.

Analysis of data

The data were statistically evaluated by analysis of variance (ANOVA) followed by Student's t-test for paired samples when comparing two populations with each other. Comparisons of subsequent interventions with controls were made using a one-way analysis of variance, followed by a Duncan's multiple range test [25]. Differences were considered significant when $P < 0.05$.

Results

Vascular responses to transmural electrical stimulation and norepinephrine

Transmural ES (1–32 Hz) produced an increase in isometric tension of mesenteric artery and vein rings. Exposure to sevoflurane (2.3% and 4.6%) did not affect the contractile responses of arteries at any frequency (Fig. 1a). Sevoflurane, however, attenuated the responses to 8 and 32 Hz in veins in concentration-dependent fashion (Fig. 1b).

Sevoflurane (2.3% and 4.6%) had no significant effect on the concentration-response curves to norepinephrine in the arteries (Fig. 2a) and veins (Fig. 2b). Transmural ES and NE produced maximum responses of about the same magnitude. The norepinephrine concentration that elicited approximately 50% of maximal tension development was 3×10^{-6} in arteries and veins.

Direct effects of sevoflurane on endothelium-intact and denuded arteries

At stable precontraction induced by NE (3×10^{-6} M), when sevoflurane was present in the bathing medium, endothelium-intact artery rings showed significant contraction at 1.7% and 3.4%, followed by relaxation at 5.1%. After discontinuation of 5.1% sevoflurane, tension increased to a degree greater than the maximal tensions produced by 3.4% sevoflurane exposure (Figs. 3 and 4a).

In contrast, in endothelium-denuded arteries, sevoflurane produced a slight relaxation (not statistically significant) at 1.7% and significant relaxation

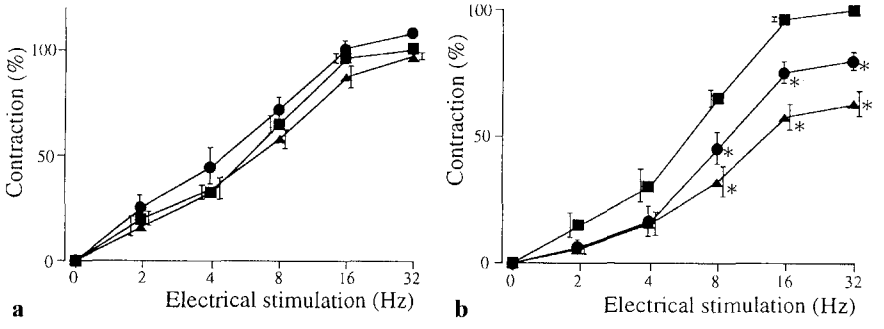

Fig. 1. Effect of sevoflurane (filled squares, 0%; filled circles, 2.3%; filled triangles, 4.6%) on responses of mesenteric arteries (**a**) and veins (**b**) to transmural nerve stimulation. Responses to 32-Hz stimulation without sevoflurane in the arteries (2.41 ± 0.22 g) and veins (3.16 ± 0.94 g) are taken as the maximum, and other data are plotted as percentages of it. Points represent the mean ($n = 6$ or 7) and vertical lines show SEM. *Significantly ($P < 0.05$) different from the corresponding value without sevoflurane

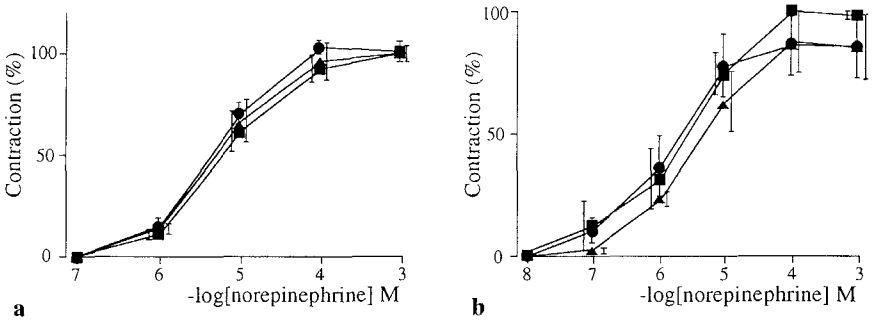

Fig. 2. Effect of sevoflurane (filled squares, 0%; filled circles, 2.3%; filled triangles, 4.6%) on contractile responses to norepinephrine in mesenteric arteries (**a**) and veins (**b**). Contractions induced by 10^{-4} M norepinephrine without sevoflurane in the arteries (2.79 ± 0.31 g) and veins (3.96 ± 0.73 g) are taken as 100%, and other data are plotted as percentages of it. Points represent the mean ($n = 6$) and vertical lines show SEM. *Significantly ($P < 0.05$) different from the corresponding value without sevoflurane

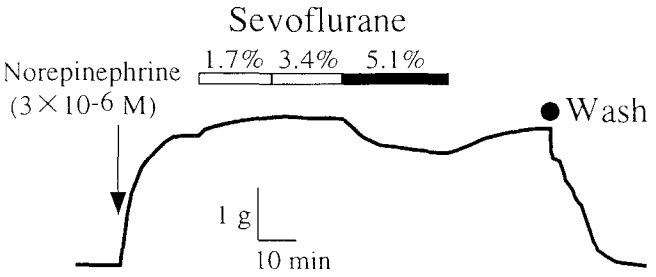

Fig. 3. Sample tracing of endothelium-intact artery exposed to increasing concentrations (1.7%, 3.4%, 5.1%) of sevoflurane

at 3.4% and 5.1%. The tension increased after discontinuation of sevoflurane to the level similar to that observed at delivery of 1.7% sevoflurane, but the tension was not restored to the control levels obtained before sevoflurane delivery (Fig. 4a).

Direct effects of sevoflurane on veins

After a stable precontraction by NE at concentrations that produced approximately half maximal tension, exposure to sevoflurane (1.7%, 3.4%, and 5.0%) induced dose-dependent relaxation in veins with endothelium (Fig. 4b).

Discussion

Sevoflurane produces dose-related arterial hypotension in humans [1] and experimental animals [3,5,26]. The possible mechanisms for the hypotensive effect of sevoflurane are associated with its ability to depress myocardial contractility [3,5], alter autonomic nervous system activity [4], depress sympathoadrenal medullary functions concerning catecholamine secretion, and decrease peripheral vascular resistance [3]. The change in vascular resistance may be partly explained by decreased sympathetic vasoconstrictor tone or by a direct depressant effect on vascular smooth muscle or endothelium-mediated relaxation.

The current study demonstrated that sevoflurane decreased the contraction evoked by electrical stimulation in isolated canine mesenteric veins, but not in arteries. Since transmural nerve stimulation to vascular smooth muscle causes the release of norepinephrine from sympathetic nerve endings [10,27–29], these results indicate that the depressed contractions observed in the presence of sevoflurane may be due to reduced levels of NE in the synaptic clefts. Thus, it can be suggested that the peripheral venodilation produced by sevoflurane is due, in part, to decreased release of norepinephrine from postganglionic adrenergic nerve endings.

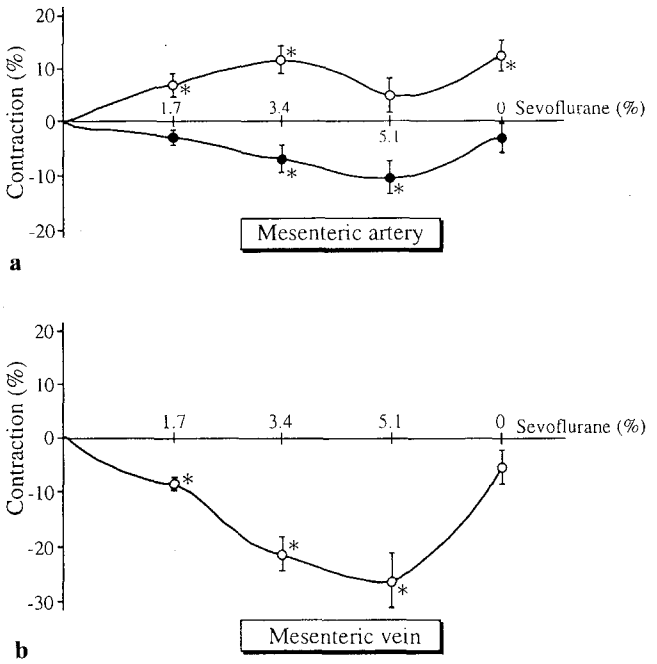

Fig. 4. a Percentage contraction or relaxation of mesenteric artery rings ($n = 5$ or 6) with (open circles) and without (filled circles) endothelium during the administration of sevoflurane and after discontinuation. The contraction induced by 3×10^{-6}M norepinephrine is taken as 100%. Data are plotted as mean ± SEM. **b** Percentage relaxation of mesenteric vein rings ($n = 6$) during administration of sevoflurane and after discontinuation. The contraction induced by 3×10^{-6}M norepinephrine is taken as 100%. Data are plotted as mean ± SEM. *Significantly ($P < 0.05$) different from the control value before sevoflurane administration

It is assumed that venous smooth muscle cells, in general, are more sensitive to the inhibitory actions of anesthetics than arterial smooth muscle cells [8]. In the present study, the effect of sevoflurane on contractile responses to ES was evident only in veins, thus suggesting that venous responses to sympathetic nerve activation are susceptible to sevoflurane. Kobayashi et al. [29] reported that in response to ES, less NE was released in the canine mesenteric artery than in the mesenteric vein. They proposed that this difference was due to anatomic differences in cleft width or the presence of a larger number of α_2- adrenoceptors mediating inhibition of NE release in the mesenteric artery than in the vein.

In contrast, sevoflurane had no effect on the contractions produced by exogenously applied NE in either arteries or veins. These results indicated that sevoflurane at the concentrations used did not interfere with postjunctional receptor-mediated contraction responses of the vessels to NE.

Generally, vascular smooth muscle contraction induced by NE is biphasic. An initial fast contraction due

principally to intracellular Ca^{2+} release is followed by a sustained contraction, which is due to entry of extracellular Ca^{2+} [20]. Sevoflurane did not affect either type of contraction induced by NE.

In the present study, we also examined the possible role of the vascular endothelium of mesenteric artery at a sustained precontraction induced by NE. It was found that increasing concentrations of sevoflurane produced a biphasic response in the endothelium-intact artery. Sevoflurane at lower concentrations produced endothelium-dependent contraction. If sevoflurane augmented the release of EDRF, it would produce vasodilation. However, in endothelium-intact artery, sevoflurane caused vasocontraction. The removal of endothelium induced relaxation in a dose-dependent fashion. Therefore, EDRF is not responsible for vasodilation by sevoflurane. However, at higher concentrations, vasodilation that is not endothelium-dependent predominates. This action is probably due to the direct relaxing effect on smooth muscle. If there were not direct relaxing effect, sevoflurane could produce more contractile response through the endothelium. This postulate is confirmed by the observation that in the absence of endothelium, sevoflurane produced dose-dependent relaxation. It seems that these results are inconsistent with a recent report that sevoflurane induced dose-dependent relaxation of isolated canine coronary artery [6]. This discrepancy was probably due to the different sensitivity of mesenteric and coronary artery to sevoflurane. There is a possibility that the direct relaxing effect of sevoflurane on coronary artery predominates over endothelium-associated contraction.

The biphasic responses to sevoflurane appear to be similar to those reported by Stones and Johns [18], suggesting that at low concentrations, enflurane and isoflurane cause vasoconstriction by inhibiting basal EDRF production and/or stimulating the release of an endothelium-derived constricting factor. The endothelial cells can release several substances, such as prostacyclin [24] and EDRF [13]. Our experimental setup does not need to test prostacyclin, because prostacyclin synthesis was inhibited by indomethacin [18,24]. The most likely candidate is basal EDRF, which is released spontaneously from endothelial cells. EDRF stimulates soluble guanylate cyclase and increases cGMP levels in smooth muscle [30]. It was recently reported that the attenuation of endothelium-dependent relaxation by halothane may be involved in interference with guanylate cyclase activation [19]. Although it is unknown whether this is true of sevoflurane, Nakamura et al. [31] reported that sevoflurane (4%) depressed levels of cGMP in rat aortae stimulated with acetylcholine and NO. The mechanism by which sevoflurane affects basal EDRF remains speculative. Our previous work [23] suggested that in the same experimental systems, sevoflurane can inactivate EDRF released by endothelium-dependent vasodilators, and the effect of sevoflurane is mediated by the generation of a closely related species of oxygen free radical. It seems likely that sevoflurane also can inactivate basal EDRF via generation of $O_2^{\cdot -}$. It has been suggested that EDRF/NO reacts with $O_2^{\cdot -}$ to produce peroxynitrite ($ONOO^-$), which decays to hydroxy radical ($HO^{\cdot}$) and nitrite radical ($NO_2^{\cdot --}$) [32–34].

The results of this study also demonstrate that sevoflurane produced vasodilation in veins with endothelium. This action could be explained by the direct inhibition of the contractile mechanisms of vascular smooth muscle. It has been demonstrated that the responsiveness to EDRF of venous tissue is less than that of arterial tissue due to differences in the ability of their endothelium to release EDRF [35]. Therefore, it is most unlikely that the relaxation of the veins is due to EDRF.

It is suggested that the relaxation of the veins by sevoflurane may be due to the inhibition of NE release from sympathetic nerve endings and to the direct inhibition of the contractile mechanisms of vascular smooth muscle. In arteries, sevoflurane causes endothelium-dependent vasocontraction, probably by inhibiting the release of basal EDRF. It is also suggested that sevoflurane can modulate the vascular tone of the arteries in the presence of normally functioning endothelium. These actions may contribute in part to understanding the mechanism of the decrease in blood pressure seen clinically during sevoflurane anesthesia.

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