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Inhibition by Enflurane of Baroreflex Mediated Mesenteric Venoconstriction in the Rabbit Ileum

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Background: **Halothane and isoflurane are known to attenuate neurally mediated regulation of mesenteric vein diameter. The current study evaluated the effects of enflurane on baroreflex control of small mesenteric veins.**

Methods: **Changes in mesenteric vein diameter, intravenous pressure, mean arterial pressure, and heart rate in response to bilateral carotid occlusion, aortic nerve stimulation, and celiac ganglion stimulation were measured in 23 chloralose-anesthetized rabbits before, during, and after 1% and 2% inhaled enflurane administration. In six other rabbits, sympathetic efferent nerve activity was recorded directly from a postganglionic splanchnic nerve, also during bilateral carotid occlusion and aortic nerve stimulation, before, during, and after inhalation of 1% and 2% enflurane.**

Results: **Baseline mean arterial pressure and heart rate decreased, and mesenteric vein diameter increased, in response to inhaled enflurane. Reflex venoconstriction and the increases in mean arterial pressure, intravenous pressure, and heart rate, in response to bilateral carotid occlusion, were significantly inhibited at both levels of inhaled enflurane. Decreases in mean arterial pressure and heart rate, and reflex venodilation in response to aortic nerve stimulation, were attenuated by 2%, but not 1%, enflurane. Mesenteric venoconstriction, blood pressure increase, and bradycardia in response to celiac ganglion stimulation were unaffected by 2% inhaled and 5% superfused enflurane. Both 1% and 2% inhaled enflurane attenuated resting and carotid sinus-mediated increases in sympathetic efferent nerve activity.**

Conclusions: **These results indicate that enflurane alters splanchnic venous reflexes in large part *via* the inhibition of sympathetic efferent activity. (Key words: Anesthetics, volatile: enflurane. Baroreceptor reflex. Capacitance. Sympathetic nervous system: mesenteric venoconstriction.)**

REFLEX regulation of mesenteric venous tone is considered to be a predominant mechanism by which acute changes in total circulatory capacitance and resistance occur.[1–4]¶ Because of this neurally mediated regulation and the ability to displace large volumes of blood, splanchnic capacitance vessels contribute greatly to overall hemodynamic stability.[3]¶ Following the report by Ozono *et al.*,[5] demonstrating active reflex venoconstriction of small mesenteric capacitance veins, other studies have shown that inhalational anesthetics, particularly halothane[6] and isoflurane,[7,8] attenuate baroreflex and chemoreflex control of splanchnic capacitance veins. These studies indicate that halothane and isoflurane alter reflex control of splanchnic venous tone and thereby interfere with the regulation and maintenance of venous return and cardiac output. Enflurane attenuates the arterial baroreceptor reflex control of heart rate in humans,[9] and depresses baseline levels of preganglionic sympathetic efferent nerve activity and reflex-induced changes in preganglionic sympathetic activity in cats.[10] A possibility of direct, peripheral action of enflurane has also been indicated.[11]

The purpose of the current study was to determine whether enflurane affects reflex control of capacitance veins in a manner similar to that demonstrated for halothane and isoflurane. Therefore, an *in situ* mesenteric vein preparation was used to examine the effects of inhaled and locally administered enflurane on neurally mediated splanchnic venoconstriction, sympathetic efferent nerve activity, and related reflex responses.

Materials and Methods

The experimental techniques used in the current study have been described in detail previously.[5,6] Animal use in the current study was approved by the Animal Care Committee of the Medical College of Wisconsin.

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¶ Hainsworth R: The importance of vascular capacitance in cardiovascular control. News in Physiological Sciences 5:250–254, 1990

Surgical Preparation

In 29 male New Zealand white rabbits (1.2 ± 0.15 kg), fasted for 24 h, anesthesia was induced with thiamylal sodium (20 mg/kg intravenously, *via* the ear vein) and maintained with α-chloralose (25 $mg \cdot kg^{-1} \cdot h^{-1}$, continuous intravenous infusion). During surgical preparation, 0.5% lidocaine was injected subcutaneously into surgical incision sites. After tracheal cannulation, ventilation was controlled with 100% O_2 using a Harvard ventilator (Model 665; Harvard Apparatus, South Natick, MA). In all rabbits, the right femoral artery and right femoral vein were catheterized and 4-cm midline laparotomy was performed. Arterial blood samples were periodically drawn to monitor blood gases and pH (ABL-1 Acid/Base Laboratory; Radiometer, Copenhagen, Danmark). The normal range of P_{O_2} (80–100 mmHg), P_{CO_2} (30–40 mmHg), and pH 7.4 were maintained by adjusting the respiration and by administering 1–2-ml boluses of sodium bicarbonate (1 meq/ml). Sodium bicarbonate (1 meq/ml) was also continuously infused with α-chloralose. Rectal temperature was measured with a thermistor probe and body temperature was maintained at 37° C with a warming blanket. In ten rabbits, both carotid arteries were isolated *in situ* for subsequent occlusion, and both aortic depressor nerves were separated and sectioned peripherally in preparation for electrical stimulation. In another group of 13 rabbits, 2 silver-wire electrodes were attached directly to the celiac ganglion, after disrupting central input to the plexus with surgical dissection and cauterization. Finally, in a separate group of six rabbits, postganglionic branches of splanchnic nerve were isolated *in situ*. Bipolar recording electrodes were glued to the isolated nerves with Wacker SilGel 604A (Wacker, Munchen, Germany) for direct recording of sympathetic efferent nerve activity (SENA).

In all rabbits, a 13-cm loop of the terminal ileum was exteriorized through laparotomy incision and positioned in a temperature-controlled plastic superfusion chamber coated with Sylgard® silicone elastomer, and mounted on a microscope stage. The ileum loop was continuously superfused with physiologic salt solution of the following composition (in mM): NaCl 118.4, KCl 5.9, $CaCl_2$ 3.3, and $NaHCO_3$ 25.[12] Physiologic salt solution was gassed with a mixture of 5% O_2, 5% CO_2, and 90% N_2, and maintained at 37° C at a pH of 7.4.

Measurements

Mesenteric Vein Diameter. The method of Bell *et al.*[13] for noncontact measuring *in situ* vascular diameter was used to determine and monitor mesenteric vein diameter. Mesentery of the externalized ileal loop was pinned to the superfusion chamber floor and the vessels were transilluminated with a Fiberoptic lamp (Model LS86/110; Fiberoptic Specialties, Palmetto, FL). Vein diameter was measured continuously using a video camera (TC 2011; RCA, Lancaster, PA) mounted on a side-arm of a Reichert Stereo Zoom microscope (Cambridge Instruments, Buffalo, NY). The video signal output was displayed on a television monitor (TC 1910; RCA, Lancaster, PA) connected to the videomicrometer system. This system converted the video signal into on-line analog output that was proportional to vein diameter.

Mesenteric Vein Pressure. Intravenous pressure was measured simultaneously with mesenteric vein diameter at the same site, using the method of Wiederhielm *et al.*[14] Glass micropipettes, with beveled 5-μm OD tips, were filled with 2M NaCl solution and used as sensing electrodes. Changes in intravenous pressure were recorded using the Servo-null micropressure system (Model 900; World Precision Instruments, Sarasota, FL).

Arterial Blood Pressure and Heart Rate. Arterial blood pressure was measured directly from the femoral artery catheter. Heart rate was derived from the arterial pressure signal.

Sympathetic Efferent Nerve Activity. Sympathetic efferent nerve activity was recorded directly from postganglionic branches of a splanchnic nerve *via* the bipolar electrodes, using a high-impedance differential preamplifier (gain 1,000×), filter amplifier (gain 1–100×), and voltage-to-frequency converter. Filtered and fully rectified nerve activity was processed using an on-line nerve averaging technique,[15] enabling analysis of nerve activity as a sum of the amplitude, frequency, and duration of depolarization bursts within the nerve bundle. Zero reference baseline for nerve activity was obtained by blocking sympathetic efferent activity with hexamethonium (10 mg/kg body weight, intravenously) at the end of each study.

All data for arterial pressure, heart rate, mesenteric vein diameter, intravenous pressure, and sympathetic efferent nerve activity were recorded on a Vetter 820 digital video cassette recorder (Vetter, Rebersberg, PA), and displayed on an Astro-Med MT9500 (Astro-Med Inc, West Warwick, RI) eight-channel recorder.

Enflurane. In each experiment, enflurane (Ethrane; Anaquest, Madison, WI) was delivered from an Ohio vaporizer (Ohio Medical Products, AIRCO, Madison, WI), with oxygen as a carrier gas at a flow rate of 5 L/

min. The nominal 0%, 1%, and 2% end-tidal concentrations of enflurane were confirmed by continuous monitoring with a mass spectrometer (Perkin Elmer 1100 Medical Gas Analyzer; Perkin Elmer, Norwalk, CT). The concentrations of enflurane in blood and physiologic salt solution were measured by gas chromatography (Perkin Elmer Sigma 3B gas chromatograph).

Experimental Protocols

Bilateral Carotid Occlusion and Aortic Depressor Nerve Stimulation. In a group of ten rabbits, changes in heart rate, mean arterial blood pressure, mesenteric vein diameter, and intravenous pressure were measured simultaneously during bilateral carotid occlusion for 30 s, and during aortic depressor nerve stimulation for 10 s (0.5 mA, 20 Hz, 1 ms pulse). The same measurements were repeated after 30 min of either 1% or 2% inhaled enflurane administration, and again after elimination of each enflurane dose (0% inhaled enflurane). The 1% and 2% enflurane doses were administered in random order and were separated by a return to 0% enflurane for 60 min.

Electrical Stimulation of Celiac Ganglion. In 13 rabbits, changes in heart rate, arterial pressure, mesenteric vein diameter, and intravenous pressure were measured during celiac ganglion stimulation (60-s stimulation, 1 ms pulses, 3–5 mA). Electrical stimulation was performed at frequencies of 5, 10, and 20 Hz, in random order, before, during, and after 2% inhaled enflurane, as described above.

To examine the possible direct effects of enflurane on small ileal mesenteric veins *in situ*, in the same group of rabbits, the responses to celiac ganglion stimulations were tested during superfusion of the mesenteric preparation with 5% enflurane equilibrated physiologic salt solution. Physiologic salt solution was equilibrated with enflurane by bubbling 5% enflurane in the 5% O_2, 5% CO_2, and 90% N_2 carrier gas mixture at a flow rate of 2 L/min for 30 min at room temperature. The resulting superfusate concentration of enflurane (1.64 ± 0.11 mM) closely approximated the blood concentration of enflurane during 30-min inhalation of 2% enflurane vapor (1.58 ± 0.07 mM). Postenflurane measurements were made after 30-min washout with enflurane-free physiologic salt solution. During superfusion experiments, the rabbit lungs were ventilated with oxygen. The order in which the inhaled enflurane and the superfused enflurane protocols were conducted was random, and at least 1 h of recovery period was allowed between the two protocols.

Sympathetic Efferent Nerve Activity Recording. In a group of six rabbits, baseline prestimulation sympathetic efferent nerve activity, as well as BCO- and ANS-related changes in sympathetic nerve activity, were recorded before, during, and after inhalation of 1% or 2% enflurane vapor.

Data Analysis

Absolute values for mesenteric vein diameter, intravenous pressure, mean arterial pressure, heart rate, and sympathetic efferent nerve activity, as well as values of percent change from control during bilateral carotid occlusion, aortic depressor nerve stimulation, and celiac ganglion stimulation, were measured before, during, and after inhalation of enflurane. All data were analyzed by multiple analysis of variance for repeated measures using ANOVA (Clear Lake Research statistical software for Apple® Macintosh™). A value of $P < 0.05$ was accepted to indicate statistical significance of the data.

Results

Bilateral Carotid Occlusion and Aortic Depressor Nerve Stimulation (ANS)

Under control (preenflurane) conditions, bilateral carotid occlusion produced reflex increases in arterial blood pressure and heart rate, as well as reflex mesenteric venoconstriction and intravenous pressure increases. Heart rate increased from 275 ± 4.6 beats/min (bpm) to 294 ± 4.4 bpm (7.0%); mean arterial pressure increased from 72 ± 1.7 mmHg to 102 ± 3.0 mmHg (42%); mesenteric vein diameter decreased from 710 ± 36 μm to 662 ± 31 μm (7.0%); and intravenous pressure increased from 7.9 ± 0.9 mmHg to 9.2 ± 0.9 mmHg (16%). Conversely, aortic depressor nerve stimulation produced reflex decreases in arterial blood pressure and heart rate, and simultaneously measured reflex mesenteric venodilatation and intravenous pressure decrease. These change are summarized in table 1.

Effects of Inhaled Enflurane

Enflurane, in concentration of 1% (0.74 ± 0.04 mM in blood) and 2% (1.54 ± 0.11 mM in blood) produced mesenteric venodilation (fig. 1). Average resting mean arterial pressure of 75.9 ± 3.4 mmHg decreased to 53.7 ± 3.3 mmHg during inhalation of 1% enflurane, and to 33.3 ± 3.4 mmHg during inhalation of 2% enflurane. Average resting heart rate (280 ± 19 bpm) was signif-

Table 1. Control Responses to Bilateral Carotid Occlusion and Aortic Nerve Stimulation

	VD (μm)	VP (mmHg)	HR (beats/min)	MAP (mmHg)
Prestimulation	710 ± 36	7.9 ± 0.9	275 ± 4.6	72 ± 1.7
BCO	662 ± 31*	9.2 ± 0.9*	294 ± 4.4*	102 ± 3.0*
% change	7	16	7	42
Prestimulation	670 ± 38	8.5 ± 0.9	280 ± 5.2	74 ± 4.2
ANS	700 ± 40*	7.8 ± 0.9*	246 ± 8.4*	53 ± 4.7*
% change	4	8	12	28

Data are mean ± SEM; n = 10.

VD = mesenteric vein diameter; VP = intravenous pressure; HR = heart rate; MAP = mean arterial pressure; BCO = bilateral carotid occlusion; ANS = aortic nerve stimulation.

* $P \leq 0.05$, BCO and ANS *versus* prestimulation control.

icantly reduced only by 2% inhaled enflurane (255 ± 13 bpm). Both concentrations of inhaled enflurane significantly suppressed heart rate, mean arterial pressure, mesenteric vein diameter, and intravenous pressure responses to bilateral carotid occlusion (fig. 2A–D). However, only 2% inhaled enflurane attenuated the responses of heart rate, mean arterial pressure, and mesenteric vein diameter to aortic depressor nerve stimulation (fig. 3A–D). Neither 1% nor 2% inhaled enflurane had a significant effect on intravenous pressure response to aortic nerve stimulation. Effects of enflurane were reversed after 1 h of recovery at 0% inhaled enflurane. The blood concentration of enflurane after recovery was approximately 0.03 ± 0.01 mM. Mean enflurane concentrations ± SEM in blood and physiologic salt solutions are listed in table 2.

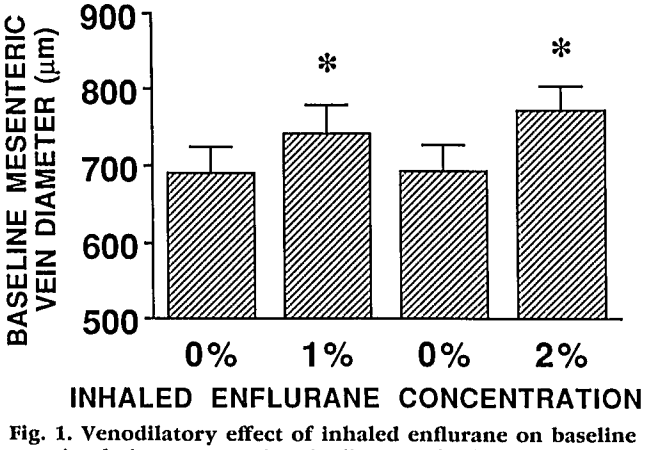

Fig. 1. Venodilatory effect of inhaled enflurane on baseline prestimulation mesenteric vein diameter (μm). Data from the BCO/ANS study. Columns represent means ± SEM; *$P < 0.05$ 1% and 2% enflurane *versus* preceding 0% enflurane; n = 10.

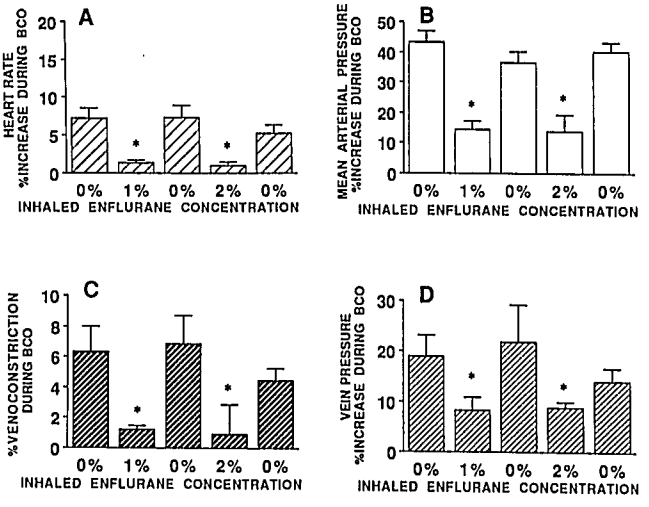

Fig. 2. Equal attenuation by 1% and 2% inhaled enflurane of the bilateral carotid occlusion (BCO)-related responses in (*A*) heart rate, (*B*) mean arterial pressure, (*C*) mesenteric vein diameter, and (*D*) intravenous pressure; *$P < 0.05$ *versus* preceding 0% enflurane; n = 10.

Celiac Ganglion Stimulation (CGS)

Graded electrical stimulation of celiac ganglion under control conditions produced, proportional to the frequency of stimulation mesenteric venoconstriction, a decrease in heart rate and an increase in arterial blood pressure (table 3). Two percent inhaled enflurane (1.58 ± 0.07 mM in blood) significantly depressed resting mean arterial pressure (from 61 ± 3.8 to 33.9 ± 4.4 mmHg) and resting heart rate (from 291 ± 9.8 to 269 ± 10.1 bpm), and attenuated the responses of

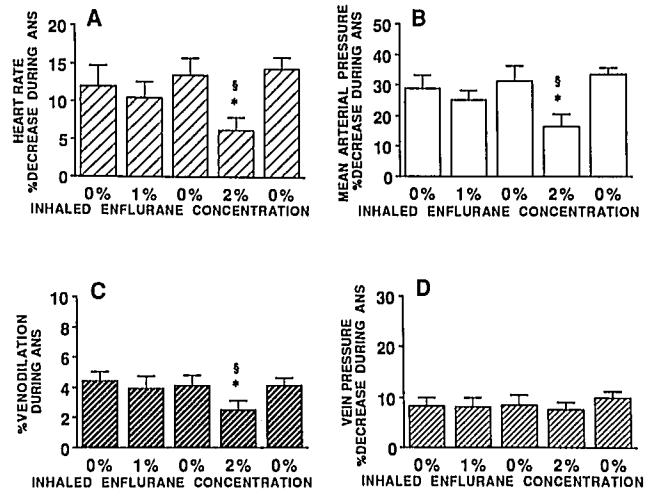

Fig. 3. Differential effect of 1% and 2% inhaled enflurane on (*A*) heart rate, (*B*) mean arterial pressure, (*C*) vein diameter, and (*D*) intravenous pressure responses to aortic nerve stimulation (ANS); *$P < 0.05$ *versus* 0% enflurane, §$P < 0.05$ *versus* 1% inhaled enflurane; n = 10.

Table 2. Concentrations of Enflurane in Blood and PSS

Vapor Concentration	Concentration in Blood (mM)	Concentration in PSS (mM)
1% inhaled (BCO/ANS)	0.74 ± 0.04	—
2% inhaled (BCO/ANS)	1.54 ± 0.11	—
2% inhaled (CGS)	1.58 ± 0.07	—
5% dissolved in PSS	0.02 ± 0.01	1.64 ± 0.11

Data are mean ± SEM. For inhaled enflurane protocols (BCO/ANS, n = 10; and CGS, n = 13) concentrations in blood are reported. For superfused enflurane protocol, concentrations in superfusate and in blood are reported (n = 13).

PSS = physiologic salt solution; BCO = bilateral carotid occlusion; ANS = aortic nerve stimulation.

heart rate and mean arterial pressure to CGS (fig. 4A and B). However, 2% inhaled enflurane had no effect on intravenous pressure response to CGS (Fig. 4C) and venoconstriction in response to graded CGS (fig. 5A). Superfusion of the mesenteric preparation with physiologic salt solution equilibrated with 5% enflurane (2.11 ± 0.12 mM enflurane in stock solution and 1.64 ± 0.11 mM enflurane in superfusate) affected none of the following: resting heart rate, mean arterial pressure, intravenous pressure and vein diameter (data not shown), and the responses to celiac ganglion stimulation (data for vein diameter are shown in fig. 5B). Blood concentrations of enflurane, measured during the superfusion experiments, were very near zero (0.02 ± 0.006 mM), reflecting little or no systemic uptake of enflurane from the superfusate.

Sympathetic Efferent Nerve Activity

Bilateral carotid occlusion resulted in a reflex increase in sympathetic efferent nerve activity. The response of sympathetic efferent nerve activity to aortic depressor nerve stimulation was characterized by initial complete inhibition of nerve activity, lasting an average

Table 3. Control Responses to Graded Celiac Ganglion Stimulation

CGS	VD (μm)	VP (mmHg)	HR (beats/min)	MAP (mmHg)
Prestimulation	836 ± 30	8.4 ± 1.1	291 ± 9.8	61 ± 3.9
5 Hz	792 ± 27	8.3 ± 1.1*	275 ± 10	66 ± 3.6*
% change	5	1.2	5.5	8
Prestimulation	824 ± 29	8.6 ± 0.9	290 ± 10	61 ± 3.7
10 Hz	733 ± 27*	8.2 ± 1.0*	268 ± 10*	72 ± 3.2*
% change	11	4.6	7.6	18
Prestimulation	842 ± 33	8.6 ± 0.9	294 ± 8.2	60 ± 4.0
20 Hz	695 ± 25*	8.1 ± 1.0*	264 ± 9.0*	76 ± 2.7*
% change	18	5.7	10.2	27

Data are mean ± SEM; n = 13.

CGS = celiac ganglion stimulation; VD = mesenteric vein diameter; VP = intravenous pressure; HR = heart rate; MAP = mean arterial pressure.

* $P \leq 0.05$ *versus* prestimulation control.

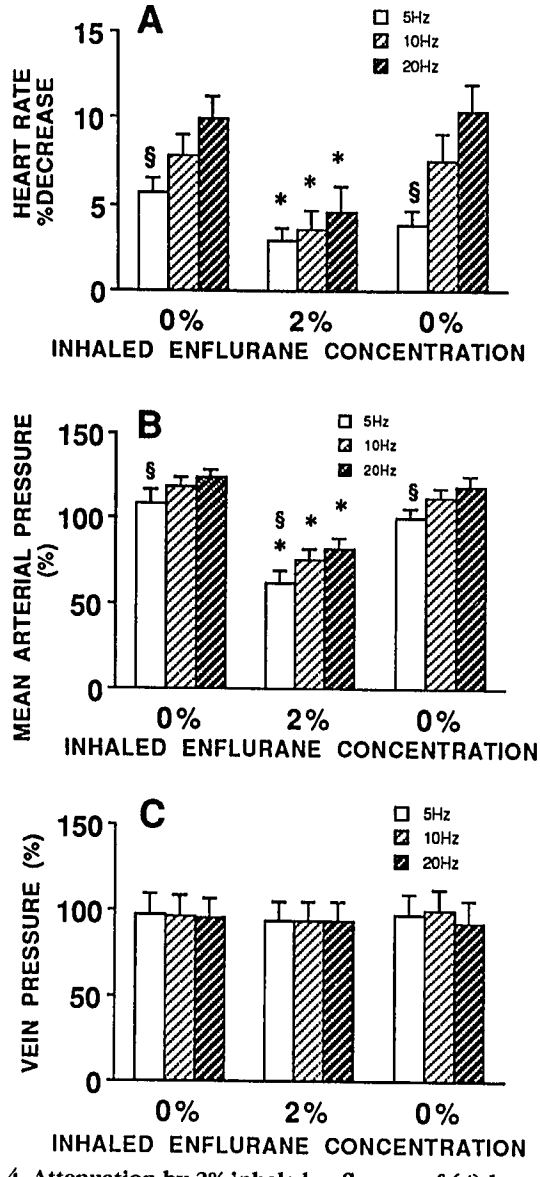

Fig. 4. Attenuation by 2% inhaled enflurane of (*A*) heart rate and (*B*) mean arterial pressure responses to graded celiac ganglion stimulation (CGS); §$P < 0.05$ 5 Hz *versus* 10 and 20 Hz, *$P < 0.05$ *versus* corresponding 0% enflurane. No significant change in (*C*) vein pressure response to CGS; n = 13.

6 s, after which it returned to baseline level. Both 1% and 2% inhaled enflurane doses (0.75 ± 0.06 and 1.59 ± 0.1 mM in blood, respectively) significantly suppressed prestimulation baseline nerve activity and attenuated characteristic changes occurring in nerve activity during bilateral carotid occlusion (fig. 6) and aortic nerve stimulation. Rapid and complete recovery in nerve activity was observed after elimination of enflurane from the circulation (0.014 ± 0.007 mM en-

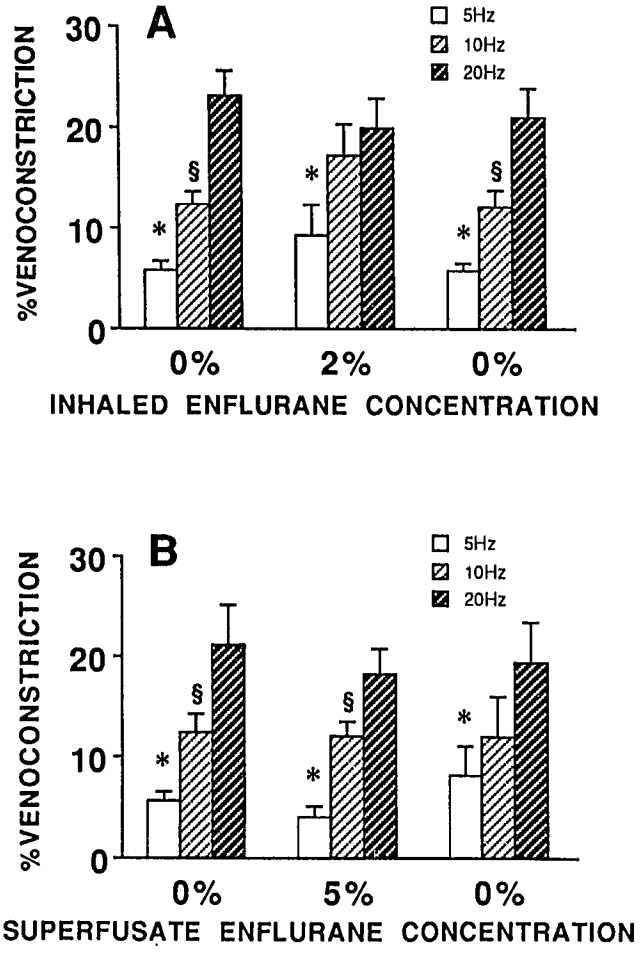

Fig. 5. (*A*) No attenuation by 2% inhaled enflurane of the stepwise increase in mesenteric venoconstriction in response to graded CGS. (*B*) Lack of effect of 5% enflurane-equilibrated superfusate on the increase in mesenteric venoconstriction in response to frequency step increases in CGS. §$P < 0.05$ 10 Hz *versus* 5 and 20 Hz, *$P < 0.05$ 5 Hz *versus* 10 and 20 Hz; n = 13.

flurane in blood). The examples of recordings of raw and averaged splanchnic nerve activity are shown in fig. 7.

Discussion

The cardiovascular effects of enflurane anesthesia have been extensively studied in humans and in experimental animals.[16] Enflurane, administered in anesthetic concentrations, produces circulatory depression[17] characterized by a direct depression of myocardial contractility,[18] resulting in reductions in the arterial blood pressure and cardiac output.[19] Enflurane also alters intestinal vascular tone[11] and reduces splanchnic and hepatic blood flow.[20] The majority of studies investigating the cardiovascular effects of enflurane have indicated lack of apparent effect of this anesthetic on systemic vascular resistance.[18,21,22] Two reports, however, have demonstrated enflurane-mediated attenuation of systemic vascular resistance, one in humans[23] and the other in chronically instrumented dogs.[24] Cardiovascular effects of enflurane can be, in part, related to the suppression of sympathetic discharge *via* the attenuation of the medullary vasomotor center,[10] the inhibition of sympathetic ganglionic transmission, and the inhibition of catecholamine release from the adrenal medulla.[25] Kobayashi *et al.* recently proposed that enflurane may directly affect vascular smooth muscle by inhibiting norepinephrine release from sympathetic nerve endings and by impeding the interaction between norepinephrine and postjunctional α_1-adrenergic receptors in vascular smooth muscle.[26]

Numerous studies have demonstrated an inhibitory effect of inhaled anesthetics on autonomic reflexes involved in cardiovascular regulation.[27] The purpose of the current study was to examine the effects of enflurane on carotid sinus-mediated control of small mesenteric capacitance veins of the rabbit ileum.

In the current study, all of the experimental protocols and responses, including control responses, were measured in rabbits initially anesthetized with thiamylal and maintained under constant α-chloralose anesthesia. α-Chloralose has been extensively used in cardiovascular studies and is recognized to provide a stable level of anesthesia while having minimal effect on cardio-

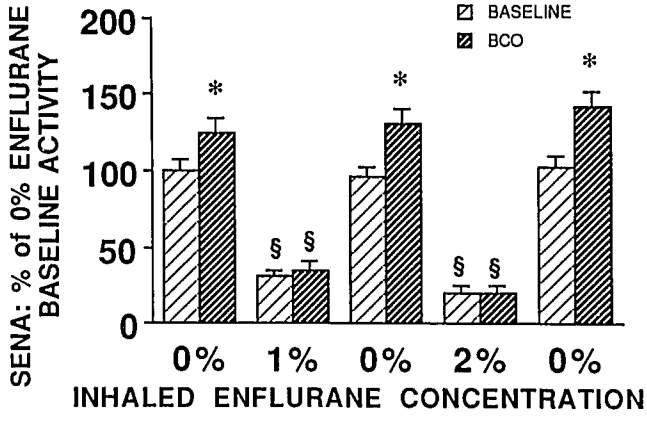

Fig. 6. Equal attenuation by 1% and 2% inhaled enflurane of both, prestimulation baseline sympathetic efferent nerve activity (SENA) and its response to bilateral carotid occlusion (BCO). *$P < 0.05$ nerve activity during BCO *versus* prestimulation baseline activity, §$P < 0.05$ *versus* preceding 0% enflurane; n = 6.

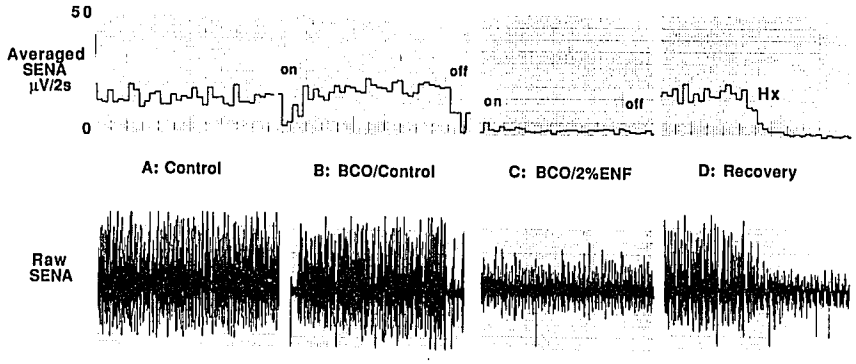

Fig. 7. Representative recordings of averaged and raw sympathetic efferent nerve activity (SENA): (*A*) baseline control nerve activity at 0% enflurane; (*B*) increase in nerve activity during control bilateral carotid occlusion; (*C*) attenuation by 2% inhaled enflurane of baseline sympathetic nerve activity and its response to bilateral carotid occlusion (BCO); and (*D*) nerve activity after recovery at 0% enflurane, and inhibition of nerve activity by hexamethonium (Hx; 10 mg/kg intravenously).

vascular reflexes.[28,29] Thus, any changes resulting from enflurane anesthesia were considered to be superimposed on, but independent of, the effects of baseline α-chloralose anesthesia. Nevertheless, in experiments involving the use of multiple anesthetic agents, a possibility of anesthetic interactions must be considered. As already mentioned, α-chloralose is known to preserve or even augment cardiovascular reflexes.[30,31] However, when combined with inhalational anesthetics, α-chloralose may depress cardiovascular reflexes. For example, a decrease in carotid sinus reflex responses was demonstrated during halothane and chloralose anesthesia in dogs.[32,35] Similarly, a combined phenobarbital and halothane anesthesia was shown to inhibit chemoreceptor mediated responses to nicotine in canine veins.[34] Though unlikely, in the current study, part of the depressant effect of enflurane could have resulted from the combined effects of enflurane and α-chloralose, and residual effects of thiamylal.

The current study demonstrated that inhaled enflurane depresses resting arterial blood pressure, heart rate, and sympathetic efferent nerve activity, and produces vasodilation of small mesenteric capacitance veins. The inhibitory effect of enflurane on splanchnic nerve activity was rather dramatic. Resting splanchnic nerve activity was reduced approximately 70–80% in the presence of both 1% and 2% inhaled enflurane. The inhibitory effect of enflurane on sympathetic efferent nerve activity is similar to what has been previously reported with halothane and isoflurane in similar experimental conditions.[6,8] In contrast to enflurane, however, these anesthetics demonstrated more dose-dependent differences. Inhaled 0.75% and 1.5% isoflurane inhibited sympathetic efferent nerve activity by 20% and 40%, respectively,[8] while inhaled 0.5% and 1.0% halothane reduced baseline sympathetic efferent nerve activity by 10% and 30%, respectively.[6] The enflurane-mediated attenuation of baseline sympathetic efferent nerve activity is in agreement with previous studies indicating that enflurane acts *via* the inhibition of central autonomic regulatory control.[10] The 43% reduction in resting mean arterial pressure in the presence of 2% inhaled enflurane is similar to what was found for 1.5% inhaled isoflurane in previous studies.[8] Such a dramatic decrease in mean arterial pressure raises a question of the overall function of experimental animals, and effects on the cerebral blood flow, as well as peripheral organ perfusion. Nevertheless, Sperry *et al.*[35] recently addressed the problem of regional blood flow in rats during deliberate hypotension combined with deep isoflurane anesthesia and/or hypovolemia. The results of this study indicate that hypotension (approximately 38% decrease in mean arterial pressure) induced during isoflurane anesthesia does not affect cerebral blood flow. Brain blood flow decreased during isoflurane anesthesia only when hypovolemia (20%) accompanied hypotension (59% decrease in mean arterial pressure). Based on these data, the maximum depression of mean arterial pressure of 43% in the presence of 2% inhaled enflurane should not have affected cerebral blood flow and brain perfusion and, therefore, it should not have influenced the carotid sinus-related reflex responses. Both 1% and 2% inhaled enflurane significantly attenuated the bilateral carotid occlusion-related reflex change in heart rate, blood pressure, sympathetic nerve activity, and mesenteric vein diameter; however, only 2% inhaled enflurane attenuated the responses to the ANS. Such differential effects of volatile anesthetic on the ANS and bilateral carotid occlusion-related reflex responses were consistent with what was observed in the isoflurane study in a similar experimental setting.[8] These results suggest that the ANS-related afferent vagal excitation may be a stronger stimulus than bilateral carotid occlusion, and, therefore, may be relatively more resistant to low concentrations of inhaled anesthetics. Reflex venodilation,

bradycardia, and hypotension in response to the ANS may also be preserved in the presence of low doses of inhaled anesthetic because of partial withdrawal of sympathetic tone. However, the attenuation of reflex responses to the ANS, in the presence of high anesthetic concentrations, indicates the inhibition of transmission at other sites of this cardiovascular reflex arc. In the current study, as in previous studies of halothane[6] and isoflurane,[8] the attenuation of reflex increase in blood pressure, heart rate, and reflex-mediated venoconstriction, in response to the BCO-induced carotid sinus hypotension, closely correlates with the inhibition of sympathetic efferent activity. These results are in agreement with other studies demonstrating vasodilatory effects of enflurane in the intestinal vascular bed. Systemic, as well as local, intraarterial administration of enflurane produced a decrease in the intestinal vascular tone in normal and denervated jejunum of the cat.[11] These studies have indicated that enflurane may not only interact with sympathetic vasomotor discharge when inhaled, but, when applied intralumenally, may reduce vascular tone through a local site of action. In contrast to the inhibitory effects of inhaled enflurane, the superfusion of mesentery with 5% enflurane equilibrated physiologic salt solution had little effect on mesenteric vein diameter. Lack of venodilatory effects of enflurane, administered to the serosal surface of the vasculature, may be associated with its relatively low tissue uptake and retention. The current and previous studies[11] suggest that a direct interaction of enflurane with vascular endothelium may be necessary to induce local, peripheral vasodilation. In this respect, enflurane is similar to halothane, showing no apparent venodilator effect when administered in superfusate;[6] however, both of these anesthetics differ from isoflurane, which produces a significant mesenteric venodilation in similar experimental conditions.[8] In the current study, the constriction of small mesenteric veins occurring in response to electrical stimulation of the celiac ganglion was not affected by inhaled or locally applied enflurane. This may be due to the fact that direct electrical activation of sympathetic postganglionic neurons may overcome any inhibitory effect of enflurane on neurally mediated reflexes. Nevertheless, the fact that inhaled enflurane clearly inhibited both venoconstriction in response to bilateral carotid occlusion and venodilation in response to aortic depressor nerve stimulation, and significantly suppressed both resting and reflex sympathetic efferent nerve activity, indicates that enflurane attenuates reflex control of splanchnic venous tone, probably *via* the central inhibitory action and, in part, proximal to the postganglionic neuron.

It is clear that the preparation used in the current study differs somewhat from the clinical setting in that there is species difference, extensive surgical preparation, basal anesthesia with systemic effects, and a possibility of different anesthetic interactions. Nevertheless, enflurane is known to attenuate sympathetically mediated reflex responses in humans, and it was the intent of this study to demonstrate that such inhibition may include venous reflexes essential for the maintenance of the overall hemodynamic stability.

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