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## ***Enflurane, Halothane, and Isoflurane Attenuate Contractile Responses to Exogenous and Endogenous Norepinephrine in Isolated Small Mesenteric Veins of the Rabbit***

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**Background:** Volatile anesthetics exert both direct and indirect (neurally mediated) effects to produce splanchnic venodilation. These effects may result in clinically relevant hemodynamic changes. The present study examined the direct effects of isoflurane, halothane, and enflurane on rabbit mesenteric venous smooth muscle.

**Methods:** Changes in isometric tension, in response to exogenous and endogenous norepinephrine, were measured in isolated mesenteric vein rings before and during the administration of volatile anesthetics.

**Results:** Exogenous and electrically evoked endogenous norepinephrine produced an increase in tension with superimposed rhythmic oscillations in tension. The exogenous norepinephrine-induced increase in tension was augmented in the presence of N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME,  $5 \times 10^{-5}$  M). The oscillatory activity was not altered by L-NAME. The increase in isometric tension in response to electrical stimulation was inhibited by phentolamine ( $5 \times 10^{-6}$  M) and tetrodotoxin ( $3 \times 10^{-6}$  M). Equianesthetic (1 MAC) concentrations of isoflurane, halothane, and enflurane significantly attenuated contractile responses to exogenous and endogenous norepinephrine, with isoflurane demonstrating a more depressant effect than halothane or enflurane. Volatile anesthetics also suppressed the amplitude and frequency of oscillations in the control as well as L-NAME-treated veins. The

inhibitory effects of volatile anesthetics on the oscillations were comparable to the effects of ryanodine, a specific blocker of calcium channels in sarcoplasmic reticulum.

**Conclusions:** These results suggest that: 1) vascular endothelium, *via* endothelium-derived relaxing factor, modulates exogenous norepinephrine responses of the venous smooth muscle; 2) the oscillatory behavior of mesenteric veins may be attributed to calcium fluxes in the venous smooth muscle cells; and 3) the norepinephrine-dependent increases in contractile and oscillatory activity are attenuated more by isoflurane than halothane or enflurane. This indicates that volatile anesthetic-mediated splanchnic venodilation is, at least in part, due to a direct action on vascular smooth muscle as well as withdrawal of sympathetic tone. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Sympathetic nervous system, catecholamines: norepinephrine. Veins, mesenteric: isometric tension; oscillatory behavior.)

VOLATILE anesthetics alter cardiovascular stability not only *via* their depressant effect on the central and autonomic nervous system function,<sup>1,2</sup> but also by their direct effect on vascular tone in regional circulatory beds, thus inducing peripheral vasodilation and subsequent hypotension.<sup>3,4</sup> The effects of anesthetic agents on the splanchnic circulation are of particular importance since splanchnic capacitance vessels, containing about 30% of the total blood volume, are the major blood reservoir in the body. Consequently, anesthetic-induced alterations in splanchnic capacitance may seriously affect overall cardiovascular performance.<sup>5,6</sup> It has been demonstrated previously<sup>7-10</sup> that one of the direct peripheral effects of halothane is its ability to alter venous smooth muscle sensitivity and responsiveness to norepinephrine. However, only a few investigators have dealt with direct effects of enflurane or isoflurane on venous smooth muscle cell function.<sup>11</sup> Therefore, the purpose of the present study was to examine and compare the effects of equianesthetic concentrations of isoflurane, enflurane, and halothane on the contractile responses of isolated small mesenteric

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veins of the rabbit to exogenously applied and endogenously released norepinephrine.

### Methods and Materials

Twenty-five male New Zealand white rabbits weighing  $1.54 \pm 0.2$  kg were used in this study, with approval of the Institutional Animal Care Committee. The rabbits were fasted for 24 h and then anesthetized with thiamylal (20 mg/kg, *via* the ear vein). A midline laparotomy was performed, and the ileal mesentery was excised and placed in cold ( $4^\circ$  C) physiologic salt solution of the following composition (in mM): NaCl 119; KCl 4.7;  $\text{CaCl}_2$  1.6;  $\text{MgSO}_4$  1.17;  $\text{NaHPO}_4$  1.18;  $\text{NaHCO}_3$  27.8; EDTA 0.026; HEPES 5.8; and glucose 5.5. After the mesentery was pinned to Sylgard-covered Petri dish containing physiologic salt solution, small (500–800  $\mu\text{m}$  in diameter) mesenteric veins were dissected, cleaned of perivascular connective tissue, and cut into 3-mm long rings (mean weight  $0.4 \pm 0.02$  mg). Individual vein rings were threaded onto two triangles made of uncoated tungsten wire (75  $\mu\text{m}$  outside diameter), and suspended in water-jacketed, temperature-controlled ( $37^\circ$  C) tissue chambers (Radnoti Glass, Monrovia, CA), each containing 15 ml of physiologic salt solution (pH 7.4) aerated continuously with a 95%  $\text{O}_2$  and 5%  $\text{CO}_2$  gas mixture.  $\text{P}_{\text{O}_2}$ ,  $\text{P}_{\text{CO}_2}$ , and pH were measured every 30 min (ABL-1 Acid-Base Laboratory, Radiometer, Copenhagen, Denmark). Lower triangles were attached to fixed anchors, and upper triangles were connected to force displacement transducers (Grass Model FT03, Grass Medical Instruments, Quincy, MA). Changes in isometric tension were recorded using a Grass (Model 7) polygraph. After a 15-min equilibration period, vein rings were stretched progressively to the optimal point on their length-tension curve (approximately 50 mg), as determined by maximal tension developed in response to potassium (80–120 mM) at each level of stretch. The vessels were then allowed to equilibrate for an additional 120 min. Enflurane (Ethrane; Anaquest, Madison, WI), isoflurane (Forane; Anaquest, Madison, WI), and halothane (Halothane; Halocarbon Laboratories, North Augusta, SC) were administered from Ohio vaporizers. Anesthetic concentrations in the gas mixture (95%  $\text{O}_2$  and 5%  $\text{CO}_2$ ) were measured by mass spectrometry (Perkin Elmer 1100 Medical Gas Analyzer, Norwalk, CT), and in the physiologic salt solution by gas chromatography (Perkin Elmer Sigma 3B gas chromatograph). A total of 214 mesenteric vein rings were examined in two experimental groups.

In the first group, the effects of enflurane, isoflurane, and halothane on the contractile responses of mesenteric veins to exogenously applied norepinephrine were examined in 78 vein rings ( $n = 11$ ). Cumulative dose-response curves to exogenous norepinephrine (dl-Norepinephrine hydrochloride, Sigma, St. Louis, MO), in concentrations ranging from 0.02 to  $1.62 \mu\text{M}$ , were obtained in control conditions, after 15 min of exposure to enflurane, isoflurane, or halothane (approximately 0.5 and 1.0 MAC), and finally, after a 1-h recovery. Concentrations of anesthetics used in all experiments are listed in table 1. Changes in the isometric tension of the veins, as well as the amplitude and frequency of rhythmic oscillations in tension induced by exogenous norepinephrine, were measured in this group. In a group of 13 vein rings ( $n = 3$ ) cumulative dose-response curves to exogenous norepinephrine were repeated in the presence and absence of  $5 \times 10^{-6}$  M ryanodine (Calbiochem, La Jolla, CA), a selective blocker of calcium ion channels in sarcoplasmic reticulum. The possible influence of endothelium-derived relaxing factor on exogenous norepinephrine-induced contractile responses and oscillatory activity of mesenteric veins was examined in a separate group of 24

**Table 1. Effective Vol%, Millimolar (mM) Concentrations, and Equivalents of 1 MAC Values for Enflurane (ENF), Isoflurane (ISO), and Halothane (HAL)**

	n*	Mass Spec%†	Effective vol%‡	mM	MAC in Rabbits§
Exogenous NE Study					
ENF low	7	2.5	1.41	0.41	0.49
ENF high		4.3	2.47	0.72	0.86
ISO low	7	1.8	1.10	0.24	0.54
ISO high		3.5	2.30	0.50	1.13
HAL low	6	1.0	0.92	0.27	0.66
HAL high		2.0	1.69	0.50	1.22
Endogenous NE study					
ENF low	7	2.1	1.37	0.39	0.48
ENF high		4.5	2.75	0.80	0.97
ISO low	7	1.8	1.16	0.25	0.56
ISO high		3.5	2.40	0.52	1.17
HAL low	7	1.0	0.61	0.18	0.44
HAL high		2.0	1.37	0.41	0.98

\* n = number of rabbits.

† Mass spectrometry readings: anesthetic concentrations in gas phase (%).

‡ Effective vol%: the mM concentrations of anesthetics measured in the baths were converted to equivalent partial pressures in the physiologic salt solution and expressed as a percentage of these anesthetics in the gas phase.

§ 1 MAC values for volatile anesthetics in New Zealand white rabbit are as follows: enflurane 2.86%, isoflurane 2.05%, halothane 1.39%.<sup>12</sup>

NE = norepinephrine.

vein rings ( $n = 3$ ). The following experimental protocol was carried out: after control recording of the contractile and oscillatory responses to exogenous norepinephrine ( $2.5 \times 10^{-7}$  M), the rings were incubated for 20 min with N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME,  $5 \times 10^{-5}$  M). L-NAME, a selective inhibitor of vascular nitric oxide synthesis, was also present during all subsequent interventions. After 20 min, the responses to exogenous norepinephrine ( $2.5 \times 10^{-7}$  M) were measured again. Vein rings were then washed and exposed to 1.0 MAC of halothane, isoflurane, or enflurane for 15 min. Responses to exogenous norepinephrine ( $2.5 \times 10^{-7}$  M) were then recorded in the presence of the anesthetics and again after a final 60-min recovery period under control conditions.

In the second group, the effects of enflurane, isoflurane, and halothane on contractile responses of mesenteric veins to electrical field stimulation were examined in 73 vein rings ( $n = 8$ ). Platinum electrodes were mounted on either side of each vein ring and connected to a Grass SD9 stimulator through output voltage transistors. The veins were electrically stimulated using 2-ms square pulses of supramaximal intensity (10 V), at a frequency of 40 Hz, for 2 min. A 1-h recovery period was allowed between consecutive stimulations. The release of endogenous norepinephrine from adrenergic nerve terminals was verified with the neuronal blocking agent tetrodotoxin (TTX,  $3 \times 10^{-6}$  M), and with phentolamine (Regitine mesylate, Ciba-Geigy, Summit, NJ), a nonselective  $\alpha$ -adrenergic receptor antagonist. Electrical stimulations of the veins were performed in control conditions, after 15 min of exposure to enflurane, isoflurane, or halothane, and again after a 1-h recovery period.

All data obtained from the mesenteric vein rings of each rabbit were averaged and treated as a single value for one rabbit. Therefore,  $n$  refers to the number of rabbits used in the experiments, and not the number of vascular rings. Mean data values for individual rabbits were then averaged again to obtain the final mean ( $\pm$ SEM) values for the experimental groups. To simplify the presentation of data, the control (pre-anesthetic) and recovery (post-anesthetic) values, not significantly different from each other, were averaged and used as mean controls. The mean values for individual rabbits also were used in statistical analysis of the data by analysis of variance and Student's  $t$  test. Differences were considered statistically significant at a  $P$  value of less than .05.

## Results

### *Effects of Inhalational Anesthetics on Contractile Responses of Mesenteric Veins to Exogenous Norepinephrine*

Exogenous norepinephrine produced a dose-dependent increase in isometric tension of mesenteric vein rings as shown in figure 1. Rhythmic oscillations in tension occurred at norepinephrine concentrations of  $8 \times 10^{-8}$  M and higher, with oscillatory amplitude ranging from  $27.6 \pm 3.7$  mg (control isoflurane group) to  $33.4 \pm 5.8$  mg (control halothane group) and  $28.4 \pm 8.1$  mg (control enflurane group), and oscillatory frequency ranging from 0.126 to 0.138 Hz in all control groups.

Enflurane, isoflurane, and halothane significantly ( $P \leq .01$ ) attenuated contractile responses of veins to exogenous norepinephrine (fig. 2). Maximal increase in isometric tension produced by the highest concentration of exogenous norepinephrine in the enflurane group (29 rings,  $n = 7$ ) decreased from  $142 \pm 19$  mg (mean control) to  $122 \pm 16$  mg (low enflurane) and  $111 \pm 21$  mg (high enflurane). In the isoflurane group (30 rings,  $n = 7$ ), the tension decreased from  $117 \pm 15$  mg (mean control) to  $83.4 \pm 15$  mg (low isoflurane) and  $82.8 \pm 11$  mg (high isoflurane). In the halothane group (19 rings,  $n = 6$ ), the tension decreased from  $174 \pm 22$  mg (mean control) to  $150 \pm 22$  mg (low halothane) and to  $120 \pm 19$  mg (high halothane). Isoflurane at 0.5 MAC had a more depressant effect than equianesthetic doses of enflurane and halothane. Significant inhibition of the oscillatory contraction amplitude (fig. 3) and a decrease in the frequency of oscillations in tension (fig. 4) were evident in the presence of all three anesthetics. In the enflurane group, control oscillatory amplitude of  $28.4 \pm 8.1$  mg decreased to  $15.6 \pm 6.0$  mg (low enflurane) and  $8.4 \pm 2.9$  mg (high enflurane). In the isoflurane group, control amplitude of  $27.6 \pm 7.0$  mg decreased to  $11.3 \pm 2.4$  mg (low isoflurane) and  $12.4 \pm 3.4$  mg (high isoflurane). Halothane produced the strongest depressant effect, inhibiting oscillatory amplitude from  $33.0 \pm 8.9$  mg to  $9.9 \pm 4.0$  mg (low halothane) and  $2.53 \pm 2.0$  mg (high halothane). These effects were reversible after discontinuing anesthetics administration and a 1-h recovery period. The above effects of isoflurane, halothane, and enflurane on oscillatory behavior of mesenteric veins were similar to the effects of ryanodine ( $5 \times 10^{-6}$  M, 13 rings,  $n = 3$ ) inhibiting oscillatory

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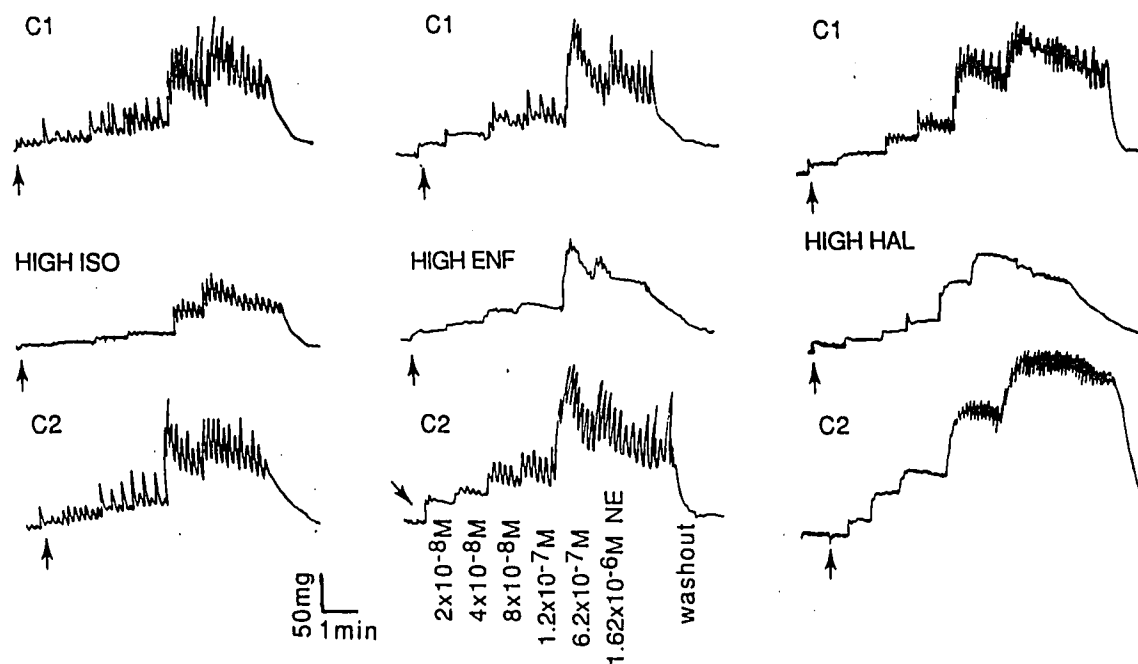


Fig. 1. Example tracings of norepinephrine dose-response curves in mesenteric vein rings obtained under control conditions (C1), during exposure of the vessels to high concentrations of enflurane, halothane, and isoflurane, (1.0 MAC), and after 1-h recovery (C2). Arrows indicate the beginning of individual cumulative dose-response curves.

amplitude and frequency but having no significant effect on total tension of the vessels (data not shown).

Pretreatment of the mesenteric vein rings with L-NAME ( $5 \times 10^{-5}$  M) augmented contractile responses to exogenous norepinephrine ( $2.5 \times 10^{-7}$  M), manifested in four- to eightfold increase in isometric tension of the veins (200–400 mg) as compared to control response (40–50 mg) to the same dose of norepinephrine. However, L-NAME had no apparent effect on exogenous norepinephrine-evoked oscillations in tension. Halothane, isoflurane, and enflurane (approximately 1.0 MAC), as well as ryanodine ( $5 \times 10^{-6}$  M), abolished rhythmic oscillations not only in control but also in all L-NAME treated vein rings. Inhibitory effects of anesthetics and ryanodine were reversed after wash-out and a 1-h recovery period (data not shown).

#### *Effects of Inhalational Anesthetics on Contractile Responses of Mesenteric Veins to Electrical Field Stimulation*

Electrical stimulation of mesenteric vein rings under control conditions produced an increase in isometric tension of  $137 \pm 24.1$  mg in the enflurane group (31

rings,  $n = 7$ ),  $145.5 \pm 10.3$  mg in the isoflurane group (26 rings,  $n = 7$ ), and  $148.3 \pm 8.3$  mg in the halothane group (16 rings,  $n = 7$ ). Seventy percent of this response was inhibited by tetrodotoxin ( $3 \times 10^{-6}$  M; 6 rings,  $n = 3$ ) and phentolamine ( $1 \times 10^{-6}$  M; 14 rings,  $n = 3$ ) and abolished by higher ( $5 \times 10^{-6}$  M) concentrations of phentolamine (fig. 5). Enflurane, isoflurane, and halothane attenuated contractile responses of mesenteric veins to electrical stimulation. Inhibitory effects of low anesthetic doses (approximately 0.5 MAC) were not statistically significant. In the enflurane group, mean basal tension decreased from  $137 \pm 24.1$  mg to  $121.7 \pm 24.3$  mg; in the isoflurane group, from  $145.5 \pm 10.3$  mg to  $121.5 \pm 10.9$  mg; and in the halothane group, from  $148.3 \pm 8.3$  to  $124.1 \pm 8.7$  mg (fig. 6). High doses of isoflurane, halothane, and enflurane (approximately 1.0 MAC) significantly ( $P \leq .01$ ) inhibited contractile responses of the veins to electrical stimulation, with isoflurane producing the most suppression of the contractile activity (decrease in tension to  $60 \pm 4.9$  mg) as compared to enflurane ( $79.1 \pm 18.9$  mg) and halothane ( $89.1 \pm 8.2$  mg). Again, these effects were reversible after termination of anesthetic administration and a 1-h period of recovery.

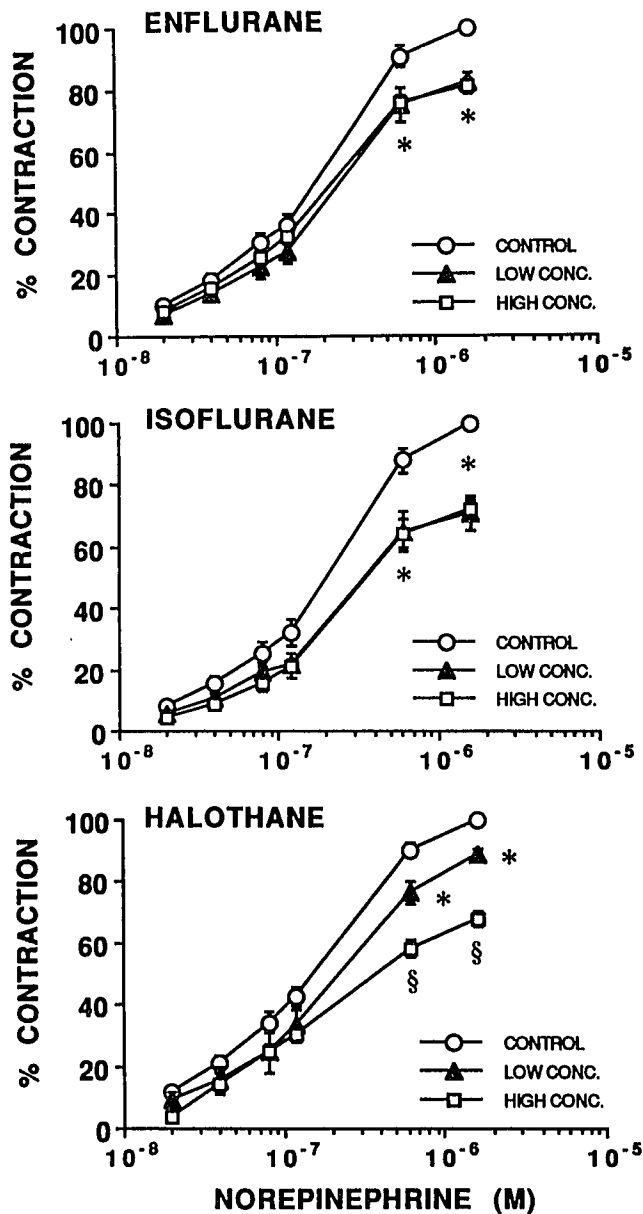


Fig. 2. Effects of enflurane, halothane, and isoflurane on contractile responses to exogenous norepinephrine in isolated mesenteric veins. Individual data points (means  $\pm$  SEM) represent the percent of maximum response, i.e., maximal increase in isometric tension induced by exogenous norepinephrine under control conditions:  $142 \pm 19$  mg in enflurane group,  $174.2 \pm 26$  mg in halothane group, and  $117 \pm 15$  mg in isoflurane group. \* $P \leq .01$  anesthetics versus control.  $\S P \leq .05$  versus control and low halothane.

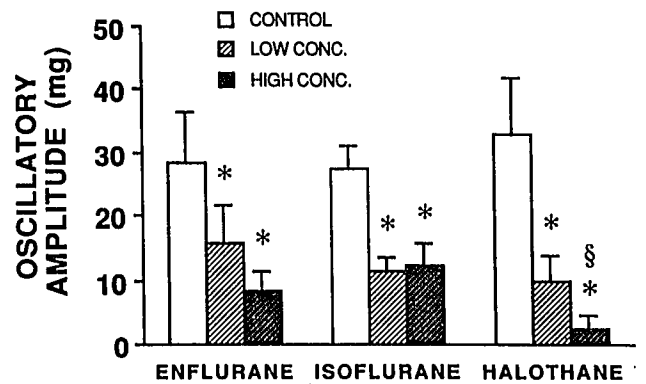


Fig. 3. The amplitude of exogenous norepinephrine-induced rhythmic oscillations in tension in mesenteric vein rings was attenuated by low and high concentrations of enflurane (29 rings,  $n = 7$ ), halothane (19 rings,  $n = 6$ ), and isoflurane (30 rings,  $n = 7$ ). \* $P \leq .01$  anesthetics versus control.  $\S P \leq .05$  high versus low enflurane, and high versus low halothane.

Discussion

Numerous investigations indicate a marked sensitivity of systemic veins to general anesthetic agents, particularly to inhaled anesthetics (for review see Altura *et al.*<sup>3</sup>). Halothane<sup>13</sup> and isoflurane<sup>14</sup> attenuate baroreceptor reflex-mediated sympathetic control of mesenteric veins. In addition, halothane induces peripheral venodilation<sup>7</sup> and attenuates venous reactivity in the systemic circulatory beds.<sup>15</sup> Enflurane<sup>16</sup> and isoflurane<sup>17,18</sup> alter vascular tone and induce vasodilation in the small intestine. The direct depressant effect of halothane<sup>19</sup> and enflurane<sup>11</sup> on venous smooth muscle function has been related to decreased venous responsiveness to norepinephrine, as well as to the in-

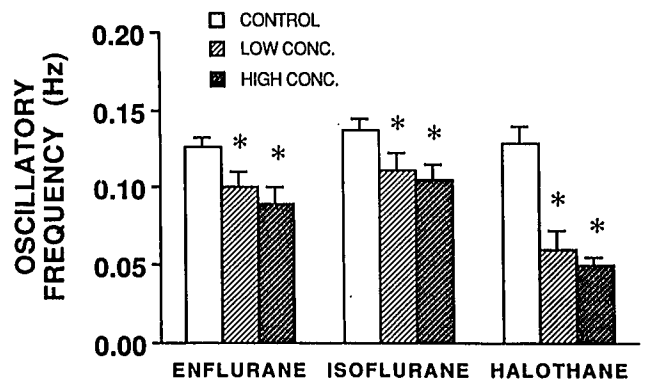


Fig. 4. Inhibition by inhalational anesthetics of the frequency of oscillations in tension in mesenteric veins. \* $P \leq .01$  anesthetics versus control; number of vein rings and rabbits in each group as in figure 3.

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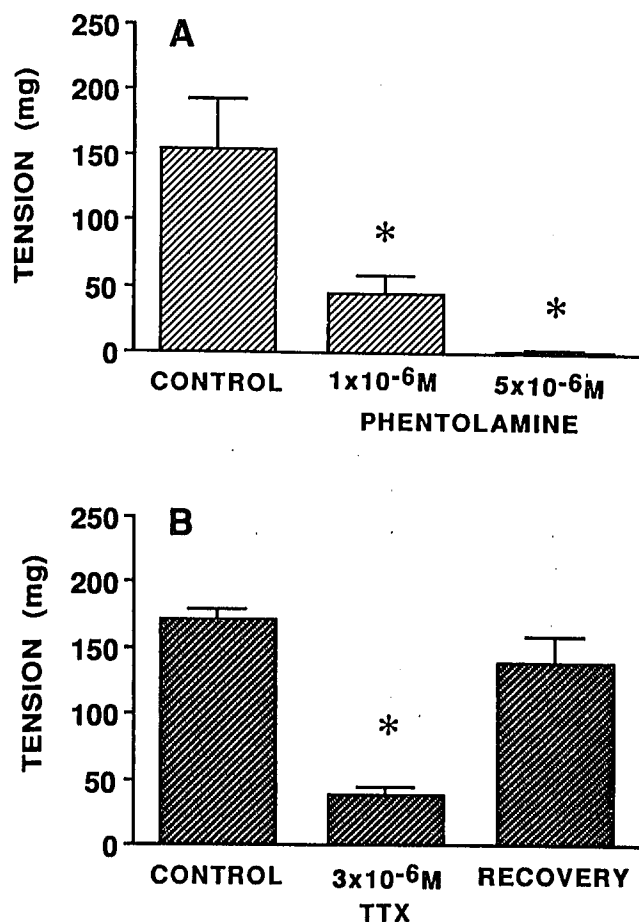


Fig. 5. Inhibition by (a) phenolamine ( $1 \times 10^{-6}$  M and  $5 \times 10^{-6}$  M, 14 vein rings,  $n = 3$ ) and (b) tetrodotoxin ( $3 \times 10^{-6}$  M, 6 vein rings,  $n = 3$ ) of contractile responses (tension, mg) to electrical stimulation in isolated mesenteric veins. \* $P \leq .01$  versus control.

inhibition of norepinephrine release from sympathetic nerve endings.<sup>9,11,20</sup>

The present study demonstrates that isoflurane, halothane, and enflurane significantly attenuate contractile responses of isolated mesenteric veins to exogenous and endogenous norepinephrine. Marijic *et al.*<sup>10</sup> reported no significant inhibition by halothane of the exogenous norepinephrine-induced increase in isometric tension in rabbit mesenteric vein rings. This discrepancy was probably due to differences in the initial resting tension applied to the vein ring preparations. Veins in general, and particularly isolated veins, are sensitive to overstretch.<sup>21-23</sup> In the previous study,<sup>10</sup> the veins were stretched to twice their resting diameter. It is possible that any response to halothane was masked by

an excessive resting tension on the vascular smooth muscle. A much lower resting tension (50 mg versus 250 mg), established for mesenteric veins in the present study, facilitated observations of small changes in tension, occurring in the presence of anesthetics. Attenuation by volatile anesthetics of the exogenous norepinephrine-mediated responses in isolated mesenteric veins indicates the possibility of a direct action of these anesthetics on the adrenergic receptors located on the venous smooth muscle. Splanchnic veins contain post-synaptic  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors.<sup>24-26</sup> Pharmacologic studies, utilizing the preparations *in situ* and *in vitro* (unpublished data from our laboratory), indicate the presence of both subtypes of  $\alpha$ -adrenergic receptor on the smooth muscle of small mesenteric capacitance veins, as these vessels show contractile responses not only to phenylephrine (a selective  $\alpha_1$ -adrenoceptor agonist), but also to BHT-933 (a selective  $\alpha_2$ -adrenoceptor agonist). It has been reported previously that, in the canine saphenous vein, the lower portion of the dose response curve to norepinephrine is mediated predominantly by  $\alpha_2$ -adrenoceptors, whereas the responses at higher concentrations of norepinephrine are mediated by  $\alpha_1$ -adrenergic receptors.<sup>25</sup> In the present study, volatile anesthetics depressed only the upper portion of norepinephrine dose-response curves. This is consistent with preferential attenuation by volatile anesthetics of  $\alpha_1$ -adrenergic receptor-mediated responses, with isoflurane and halothane demonstrating a greater effect than enflurane.

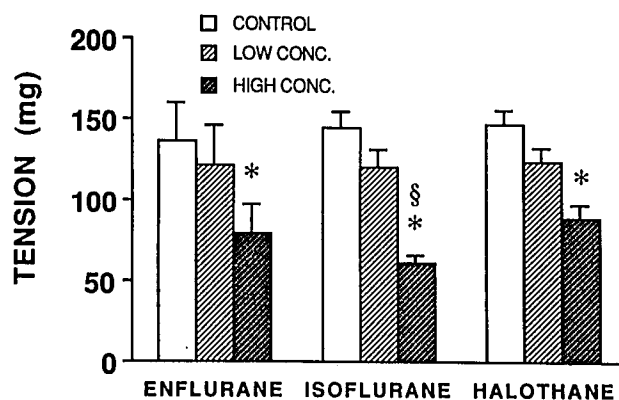


Fig. 6. Effects of enflurane (31 rings,  $n = 7$ ), halothane (16 rings,  $n = 7$ ), and isoflurane (26 rings,  $n = 7$ ) on contractile responses of mesenteric veins to electric field stimulation. Significant inhibition of isometric tension by high (approximately 1.0 MAC in rabbit) concentrations of volatile anesthetics. \* $P \leq .01$  versus control. § $P \leq .05$  high isoflurane versus high halothane and enflurane.

Oscillations in vascular tension or diameter are considered an integral component of normal vasomotion. Spontaneous or vasoactive agent-induced rhythmic oscillations in tension have been observed *in vivo* in microcirculation of nonanesthetized animals and *in vitro* in various arterial and venous preparations from normal and hypertensive animals.<sup>27,28</sup> Longitudinal and helical strips of mesenteric veins exhibit spontaneous rhythmic contractions.<sup>21</sup> Marijic *et al.*<sup>10</sup> observed exogenous norepinephrine-induced oscillations in tension in the ring preparations of rabbit mesenteric veins. These oscillations were depressed by halothane (1.5%) and completely inhibited by ryanodine. Inhibition by ryanodine indicates that the oscillatory activity of mesenteric veins is associated with intracellular calcium fluxes in which the sarcoplasmic reticulum plays an important role.<sup>29</sup> The effect of halothane suggests the possibility of this anesthetic interaction with intracellular calcium pools.<sup>30,31</sup> The results of the present study extend these observations, demonstrating that enflurane and isoflurane also attenuate norepinephrine-induced oscillations in tension, depressing the amplitude and the frequency of rhythmic oscillatory contractions. High concentrations of volatile anesthetics (approximately 1.0 MAC in the rabbit) completely inhibited oscillatory activity, as did ryanodine. Similar inhibitory effects of volatile anesthetics and ryanodine on the oscillations suggest a similar mechanism of action in both cases. However, no direct link between anesthetic actions and the actions of the ryanodine receptor has been demonstrated.

In the present study, we also examined the possible role of the vascular endothelium in the norepinephrine-induced increase in contractile tension and oscillatory activity of mesenteric veins. A marked increase in contractile responses to exogenous norepinephrine, in L-NAME-treated veins, indicates the possibility of a modulatory effect of endothelium-derived relaxing factor on norepinephrine-mediated vasoconstriction. In contrast, the lack of apparent effect of L-NAME on the oscillations suggests that the venous oscillatory behavior may not depend on endothelium-derived relaxing factor.

The exact mechanism and physiologic significance of the vascular oscillations are not fully explained. Oscillatory behavior has been attributed to altered membrane potassium and calcium fluxes.<sup>28</sup> The oscillations depend on the presence of extracellular calcium, which may in turn be influenced by alterations in the

extracellular magnesium concentrations.<sup>32,33</sup> Vascular rhythmic contractions also may reflect the functioning of cytosolic calcium oscillators relying on periodic calcium release from intracellular sites.<sup>34</sup> It has been proposed that the oscillations are involved in fine regulation of blood flow and, in the venous circulation, serve to aid venous return. The present study supports previous findings indicating that norepinephrine-dependent oscillatory activity of rabbit small mesenteric veins may be attributed to calcium fluxes in the venous smooth muscle cells and also demonstrates the attenuation by volatile anesthetics of this vascular phenomenon.

Rabbit mesenteric veins respond to electrical field stimulation with an increase in basal isometric tension.<sup>35-37</sup> This response is reversibly inhibited by phentolamine, a nonselective  $\alpha$ -adrenergic receptor antagonist, and by tetrodotoxin, a neuronal blocking agent,<sup>38-40</sup> indicating a neuronal effect occurring as a consequence of endogenous norepinephrine release from postganglionic sympathetic nerve terminals. Equianesthetic doses (approximately 1.0 MAC in the rabbit) of volatile anesthetics significantly inhibited contractile responses of mesenteric veins to electrical stimulation, with isoflurane showing a greater depressant effect on endogenous norepinephrine-induced tension than that of halothane or enflurane. The contractile responses to endogenously released and exogenously applied norepinephrine represent distinct processes. However, the greater inhibitory effect of isoflurane on endogenous norepinephrine-induced tension may indicate a particular capacity of this anesthetic to alter neuroeffector transmission between adrenergic nerve terminals and the venous smooth muscle, a capacity shared to a lesser extent with the two other volatile agents studied.

In summary, isoflurane, halothane, and enflurane attenuate contractile responses to exogenous and endogenous norepinephrine in isolated small mesenteric capacitance veins of the rabbit ileum. It is likely that these volatile agents alter agonist-dependent extracellular and intracellular calcium fluxes in the venous smooth muscle. Generally, isoflurane exerts a greater depressant effect on the norepinephrine-mediated increase in isometric tension than do halothane and enflurane, which have stronger inhibitory effects on exogenous norepinephrine-induced oscillations in tension. Attenuating vascular tension and oscillatory activity of the mesenteric veins, in part *via* a direct

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action on the venous smooth muscle, volatile anesthetics may promote changes in the venous tone and contribute to venodilation in the ileal region of the splanchnic circulatory bed.

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### References

- Clark SC, MacCannell KL: Vascular responses to anaesthetic agents. *Can Anaesth Soc J* 22:20-33, 1975
- Seagard JL, Bosnjak ZJ, Hopp FA, Kotrly KJ, Ebert TJ, Kampine JP: Cardiovascular effects of general anesthesia, *Effects of Anesthetics*. Edited by Covino BG, Fozzard HA, Rehder K, Strichartz G. Baltimore, Waverly, 1985, pp 149-177
- Altura BM, Altura BT, Carella A, Turlapaty PDMV, Weinberg J: Vascular smooth muscle and general anesthetics. *Federation Proceedings* 39:1584-1591, 1980
- Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. *Anesth Analg* 63:557-565, 1984
- Rothe CF: Reflex control of veins and vascular capacitance. *Physiol Rev* 63:1281-1342, 1983
- Hainsworth R: The importance of vascular capacitance in cardiovascular control. *News in Physiological Sciences* 5:250-254, 1990
- Muldoon SM, Vanhoutte PM, Lorenz RR, VanDyke RA: Venomotor changes caused by halothane acting on the sympathetic nerves. *ANESTHESIOLOGY* 43:41-48, 1975
- Suzuki H: Effects of endogenous and exogenous noradrenaline on the smooth muscle of guinea-pig mesenteric vein. *J Physiol (Lond)* 321:495-512, 1981
- Roric DK, Tyce GM, Mackenzie RA: Evidence that halothane inhibits norepinephrine release from sympathetic nerve endings in dog saphenous vein by stimulation of presynaptic inhibitory muscarinic receptors. *Anesth Analg* 63:1059-1064, 1984
- Marijic J, Madden JA, Kampine JP, Bosnjak ZJ: The effect of halothane on norepinephrine responsiveness in rabbit small mesenteric veins. *ANESTHESIOLOGY* 73:479-484, 1990
- Kobayashi Y, Yoshida K, Noguchi M, Wakasugi Y, Ito H, Okabe E: Effect of enflurane on contractile reactivity of isolated canine mesenteric arteries and veins. *Anesth Analg* 70:530-536, 1990
- Drummond JC: MAC for halothane, enflurane and isoflurane in the New Zealand white rabbit: And a test for the validity of MAC determinations. *ANESTHESIOLOGY* 62:336-338, 1985
- Stekiel TA, Ozono K, McCallum JB, Bosnjak ZJ, Stekiel WJ, Kampine JP: The inhibitory action of halothane on reflex constriction in mesenteric capacitance veins. *ANESTHESIOLOGY* 73:1169-1178, 1990
- McCallum JB, Stekiel TA, Ozono K, Bosnjak ZJ, Kampine JP: Isoflurane attenuates the sympathetic reflex response of *in situ* mesenteric veins in the rabbit (abstr). *Anesth Analg* 70:S260, 1990
- Morrow DH, Pierce GE: The effect of halothane on systemic venous reactivity. *J Surg Res* 8:115-121, 1968
- Henriksson BA, Biber B, Lundberg D, Martner J, Nilsson H, Ponten J: Vasodilator responses to enflurane in the small intestine. *Acta Anaesthesiol Scand* 29:287-293, 1985
- Ostman M, Biber B, Martner J, Reiz S: Effects of isoflurane on vascular tone and circulatory autoregulation in the feline small intestine. *Acta Anaesthesiol Scand* 29:389-394, 1985
- Biber B, Schaefer CF, Smolik MJ, Lawrence MC, Lerner MR, Brackett DJ, Wilson MF, Fagraeus L: Dose-related effects of isoflurane on superior mesenteric vasoconstriction induced by endotoxemia in the rat. *Acta Anaesthesiol Scand* 31:430-437, 1987
- Spiss CK, Smith CM, Tsujimoto G, Hoffman BB, Maze M: Prolonged hyporesponsiveness of vascular smooth muscle contraction after halothane anesthesia in rabbits. *Anesth Analg* 64:1-6, 1985
- Roizen MF, Thoa NB, Moss J, Kopin IJ: Inhibition by halothane of release of norepinephrine, but not dopamine- $\beta$ -hydroxylase from guinea-pig vas deferens. *Eur J Pharmacol* 31:313-318, 1975
- Sutter MC: The pharmacology of isolated veins. *Br J Pharmacol* 24:742-751, 1965
- Bevan JA: Sensitivity of the large blood vessels of the rabbit to l-epinephrine and l-norepinephrine. *Circ Res* 9:700-704, 1961
- Hall WJ, O'Connor PC: The action of vasoactive drugs on longitudinal and circular muscle of dog mesenteric vein. *J Pharm Pharmacol* 25:109-118, 1973
- Ruffolo RR, Nichols AJ: Recent experimental and conceptual advances in drug receptor research in the cardiovascular system. *Advances in Drug Research* 17:235-348, 1988
- Matthews WD, Jim KF, Heible JP, DeMarinis RM: Postsynaptic  $\alpha$ -adrenoceptors on vascular smooth muscle. *Federation Proceedings* 43:2923-2928, 1984
- Hamilton CA, Reid JL: A postsynaptic location of  $\alpha_2$  adrenoceptors in vascular smooth muscle: In vitro studies in the conscious rabbit. *Cardiovasc Res* 16:11-15, 1982
- Feletou M, Hoeffner U, Vanhoutte PM: Endothelium-dependent relaxing factors do not affect the smooth muscle of portal-mesenteric veins. *Blood Vessels* 26:21-32, 1989
- Osol G, Halpern W: Spontaneous vasomotion in pressurized cerebral arteries from genetically hypertensive rats. *Am J Physiol* 254:H28-H33, 1988
- Ashida T, Schaeffer J, Goldman WF, Wade JB, Blaustein MP: Role of sarcoplasmic reticulum in arterial contraction: Comparison of Ryanodine's effect in a conduit and muscular artery. *Circ Res* 62:854-863, 1988
- Greenberg S, Long JP, Diecke PJ: Differentiation of calcium pools utilized in the contractile response of canine arterial and venous smooth muscle to norepinephrine. *J Pharmacol Exp Ther* 185:493-504, 1973
- Blanck TJJ, Casella ES: Interaction of volatile anesthetics with calcium-sensitive sites in myocardium, *Cell Calcium Metabolism: Physiology, Biochemistry, Pharmacology and Clinical Implications*. Edited by Fiskum G. New York, Plenum, 1989, pp 581-591
- Altura BM, Altura BT: Magnesium ions and contraction of vascular smooth muscles: Relationship to some vascular disease. *Federation Proceedings* 40:2672-2679, 1981
- Szabo C, Dora E, Farago M, Horvath I, Kovach AGB: Noradrenaline induces rhythmic contractions of feline middle cerebral artery at low extracellular magnesium concentration. *Blood Vessels* 27:373-377, 1990



34. Berridge MJ, Galione A: Cytosolic calcium oscillators. *FASEB J* 2:3074-3082, 1988
35. Vanhoutte P, Clement D, Leusen I: The reactivity of isolated veins to electrical stimulation. *Arch Int Physiol Biochim Biophys* 75: 641-656, 1967
36. Bevan JA, Hosmer DW, Ljung B, Pegram BL, Su C: Innervation pattern and neurogenic response of rabbit veins. *Blood Vessels* 11: 172-182, 1974
37. Furness JB, Marshall JM: Correlation of the directly observed responses of mesenteric vessels of the rat to nerve stimulation and noradrenaline with the distribution of adrenergic nerves. *J Physiol (Lond)* 239:75-88, 1974
38. VanHelden DF: Electrophysiology of neuromuscular transmission in guinea-pig mesenteric veins. *J Physiol (Lond)* 401:469-488, 1988
39. Bevan JA, Su C: Sympathetic mechanisms in blood vessels: Nerve and muscle relationships. *Ann Rev Pharmacol Toxicol* 13:269-285, 1973
40. Holman ME, McLean A: The innervation of sheep mesenteric veins. *J Physiol (Lond)* 190:55-69, 1967