Anesthesiology
1999; 91:470-8

Specific Actions of Halothane, Isoflurane, and Desflurane on Sympathetic Activity and Aδ and C Somatosympathetic Reflexes Recorded in Renal Nerves in Dogs

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Background: **This was a study of the relative effects on directly recorded sympathetic activity of desflurane, isoflurane, and halothane.**

Methods: **Renal sympathetic nerve activity (RSNA) was recorded with bipolar electrodes in renal nerves exposed retroperitoneally in anesthetized (α-chloralose), paralyzed (succinylcholine), and artificially ventilated dogs. Somatosympathetic responses were evoked by supramaximal electrical stimulation of radial nerves (0.33 Hz, 30 V, 0.5 ms). Spontaneous and evoked activity were rectified, averaged, and integrated to allow quantitative comparison of the effects of 3–12% desflurane, 0.6–2.4% isoflurane, and 0.4–1.6% halothane.**

Results: **Increasing concentrations of isoflurane progressively depressed mean RSNA, Aδ, and C reflexes by 40% ($P < 0.01$), 50% ($P < 0.01$) and 70% ($P < 0.001$) respectively at 2.4% concentration. Halothane depressed both reflexes equally by approximately 60% ($P < 0.01$) at 1.6% concentration, without significant depression of spontaneous RSNA. Desflurane increased and subsequently decreased RSNA by 37% ($P < 0.02$) and 65% ($P < 0.001$) at concentrations of 6% and 12% respectively, and although somatosympathetic reflexes remained unchanged up to 9%, both were depressed equally by 70% ($P < 0.01$) at 12% concentration.**

Conclusion: **After equilibration, lower concentrations of desflurane remained excitatory, but, like isoflurane, higher concentrations depressed RSNA. The effect of halothane on RSNA was insignificant. Isoflurane depressed C more than Aδ somatosympathetic reflexes, which is uncorrelated with lipid solubility because desflurane and halothane, which have the highest and lowest minimum alveolar concentration, respectively, depressed both equally. (Key words: Desflurane; halothane; isoflurane; mechanisms of anesthesia; nociceptive reflex; sympathetic activity.)**

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Received from the Department of Anesthetics and Intensive Care, Imperial College School of Medicine, Hammersmith Hospital, London, United Kingdom. Submitted for publication April 13, 1998. Accepted for publication March 24, 1999. Support was provided solely from institutional and/or departmental sources.

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INHALATIONAL agents at relatively low concentrations obtund reflex motor responses to noxious stimuli,[1,2] but higher concentrations are required to depress an increase in plasma catecholamine concentrations during surgery.[3,4] Attenuation of sympathoexcitation induced by surgical stimulation with better hemodynamics may improve perioperative outcome.[5-7] Hence, studies of the relative effects of anesthetic agents and techniques on the sympathetic nervous system remain an important area of research.

Preliminary observations reported that whereas desflurane caused similar depression of both Aδ and C fiber-mediated somatosympathetic reflexes, isoflurane produced a relatively greater depression of C compared with Aδ reflexes,[8] which has also been reported for sevoflurane.[9] If the greater effect of these anesthetics on C reflexes is caused by their relatively greater lipid solubilities compared with desflurane, then halothane, the most lipid-soluble of the current clinically available anesthetic vapors, would be expected to show an even greater effect on C compared with Aδ reflexes. This hypothesis was tested by comparing the effects of desflurane, isoflurane, and halothane on spontaneous and reflex sympathetic activity.

Material and Methods

General Procedures

The study was approved by the UK Home Office (License PPL 90/00852). Fifteen beagles (17.0-20.0 kg) were anesthetized with methohexital (15 mg/kg

intravenously) followed by 1% α-chloralose in an initial bolus dose of 30 mg/kg intravenously followed by a continuous infusion of 17–20 mg · kg^{-1} · h^{-1}.[10] The lungs were ventilated (SLE 2000 ventilator; SLE Ltd., Croydon, UK) *via* a cuffed tracheal tube with oxygen enriched air. A femoral artery and vein were cannulated. Bolus doses of succinylcholine (10 mg intravenously) were repeated at 30-min intervals to maintain muscle paralysis, for example during electrical stimulation of radial nerves. The depth of anesthesia was assessed by the presence of floppy ears and the absence of spontaneous movements and the glabellar reflex when succinylcholine was temporarily withheld at intervals of approximately 90 min. The esophageal temperature was measured with a thermistor (Yellow Springs Instruments, Yellow Springs, OH) and was maintained between 37 and 38°C. The arterial *p*H, carbon dioxide tension, and oxygen tension were measured with a Radiometer (Copenhagen, Denmark) ABL3 blood gas analyzer, and the values were maintained constant and within the ranges 7.3–7.4, 36–40 mmHg, and 180–210 mmHg, respectively. A pulmonary-artery flotation catheter (5-French gauge) was inserted *via* the right external jugular vein. The mean systemic, central venous, and pulmonary artery pressures and heart rate were recorded continuously using a heated stylus recording system (Devices M19, Hertfordshire, UK). Cardiac output was measured in duplicate at end-inspiration by thermodilution, and again if the two measurements differed by more than 10%.

Nerve Stimulation and Recording of Sympathetic Activity

A short section of the lateral superficial branch of the radial nerve in the left foreleg was exposed, dissected free from surrounding tissues, desheathed, cut distally, and mounted on silver electrodes in warm mineral oil (37°C). Repeated single electrical stimuli (0.33 Hz, 30 V, duration 0.5 ms) were applied to the radial nerve using a Grass (Quincy, MA) S88 stimulator with matching isolation units (Grass 478A).

Single fascicles of the renal sympathetic nerves, exposed retroperitoneally adjacent to the renal artery close to the kidney, were isolated, desheathed, cut distally, and mounted on silver electrodes in mineral oil. Signals from the renal sympathetic nerves were preamplified (Tektronix 122 preamplifier, Beaverton, OR). Twenty-second periods of sympathetic activity from a continuous recording were processed, subjected to full-wave rectification, and integrated with a time constant of 100 ms (Neurolog NL90 multifunction system, Welwyn Garden, Hertfordshire, UK). The evoked responses were averaged (×16), rectified and integrated (Neurolog NL90).

Administration of Inhalational Anesthetics and Experimental Protocol

After surgery, each preparation was allowed to stabilize for at least 30 min before measurements were processed, and measurements were repeated 30–45 min later to ensure continuing stability. The second data set was used as the control. The dogs were randomly allocated to receive one of the three inhalational anesthetics. Desflurane was delivered from a Tec 6 heated vaporizer (Ohmeda, West Yorkshire, UK) and isoflurane and halothane from Fortec and Fluotec 4 vaporizers, respectively (Cyprane, Keighley, UK). The end-tidal concentrations of the agents were measured at the proximal end of the tracheal tube with an infrared analyzer (Capnomac II, Datex, Helsinki, Finland), which was calibrated with standard commercially available gas mixtures (Quick cal, Datex, Helsinki, Finland).

Each anesthetic was administered to five dogs, desflurane at 3%, 6%, 9%, and 12%; isoflurane at 0.6%, 1.2%, 1.8% and 2.4%; and halothane at 0.4%, 0.8%, 1.2%, and 1.6% end-tidal concentrations. Following each change in inspired concentration, after rapid equilibration to a constant end-tidal concentration, the anesthetic was administered for another 20 min before further measurements were processed. After withdrawal of the anesthetics, observations were made for a further 60 min, during which recovery occurred, confirming the absence of significant changes in baseline values.

Data Processing

The total electrical activity in multifiber recordings of RSNA was processed as the areas within the recorded envelopes of rectified integrated spontaneous activity and averaged, rectified,and integrated evoked responses, expressed in arbitrary units and presented as a percentage of control values. The average of three measurements was used for each data set. The integral of the average of the groups of rectified signals is a voltage-by-time envelope (20 s for spontaneous activity and 250–400 ms for Aδ and 350–500 msec for C responses) and is therefore expressed in arbitrary units. The time base remained the same throughout these experiments because of the similar sizes of the dogs and also the length

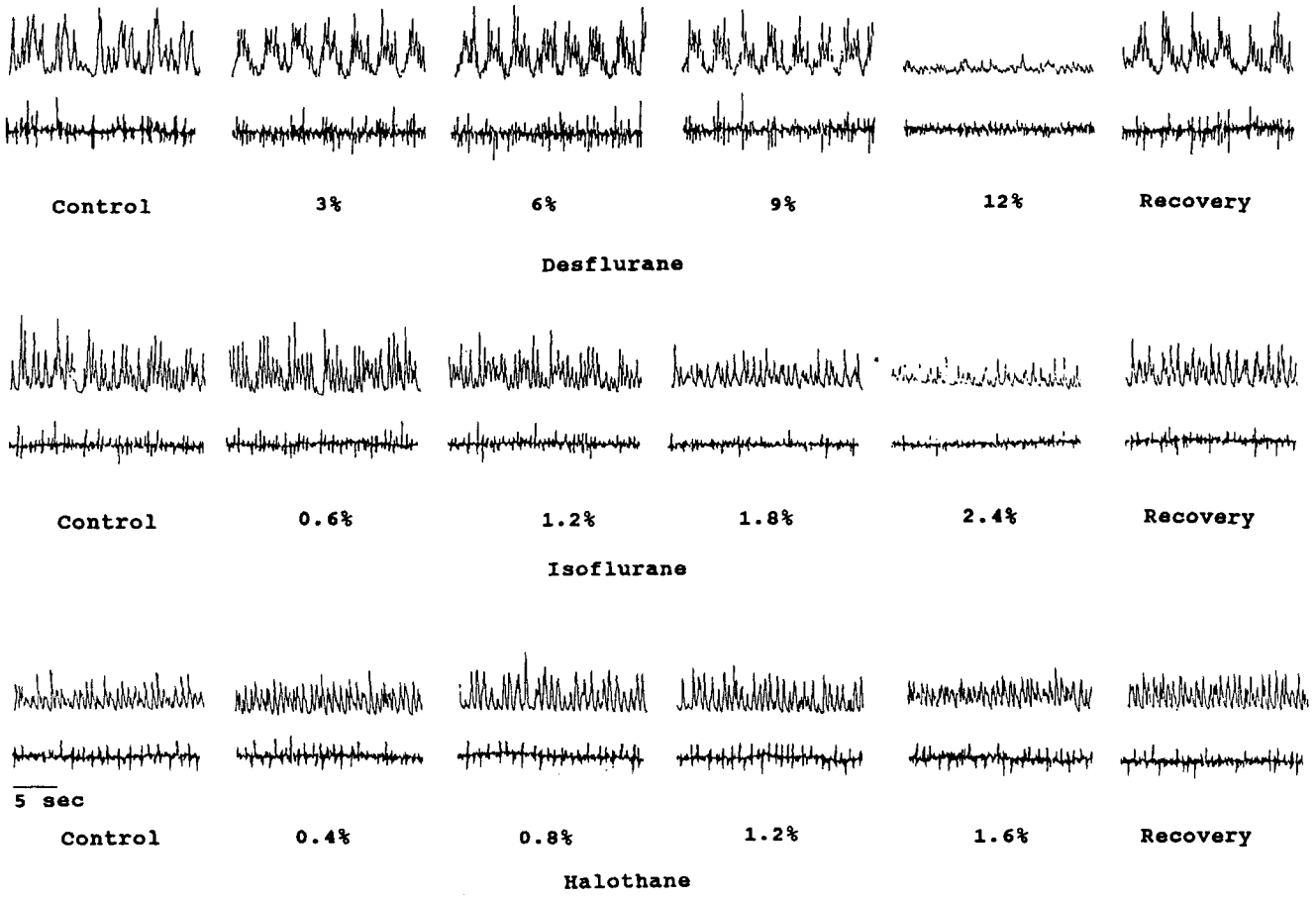

Fig. 1. Typical multifiber recordings of spontaneous renal sympathetic activity in dogs at increasing end-tidal concentrations of inhalatonal anesthetics. (*Top*) Desflurane. (*Middle*) Isoflurane. (*Bottom*) Halothane. In each case, lower traces are the direct recording, upper traces are the rectified and integrated signal for quantitative comparison.

of the afferent pathway. The heights of the envelopes of activity for different experiments were adjusted to be approximately the same. Hence the control values, in arbitrary units, were in narrow bands for RNSA and Aδ and C somatosympathetic reflexes. After setting up, both the gain of recording system and the time base had to remain unchanged; otherwise the data would have become invalid.

Analysis of Data

For each agent studied, data for Aδ and C evoked somatosympathetic reflexes, RSNA, and hemodynamic variables were compared with control values using analysis of variance followed by paired *t* tests if appropriate. For the relative effects on Aδ and C reflexes, analysis of variance followed by unpaired *t* tests was applied. $P <$ 0.02 was considered significant. All data are expressed as mean ± SD.

Results

Figures 1 and 2 show typical recordings of the effects of desflurane, isoflurane, and halothane on RSNA and Aδ and C fiber-mediated somatosympathetic reflexes in single preparations.

Control Data for Sympathetic Activity

The control data, in arbitrary units, for spontaneous activity and Aδ and C reflexes (mean ± SD) were for halothane: RSNA 6.6 ± 2.2, Aδ 3.3 ± 0.4, and C 2.5 ± 0.5; for isoflurane: RSNA 6.5 ± 1.7; Aδ 3.1 ± 0.7, and C

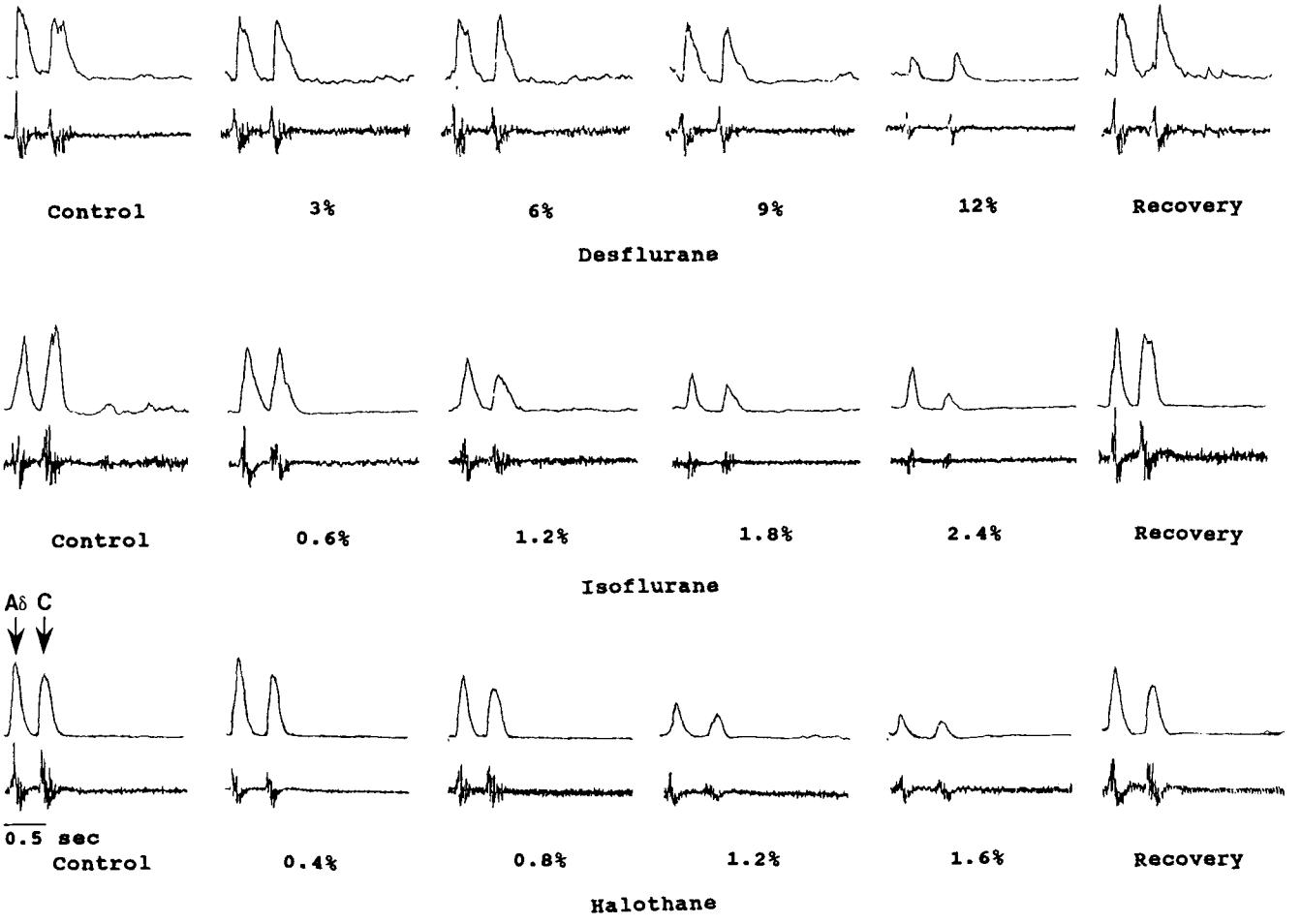

Fig. 2. Typical recordings from renal sympathetic nerves of somatosympathetic reflexes evoked by repeated single supramaximal electrical stimulation (30 V, 0.5 ms, 0.33 Hz) of a radial nerve at increasing end-tidal concentrations of inhalational anesthetics. (*Top*) Desflurane. (*Middle*) Isoflurane. (*Bottom*) Halothane. First or early response and the second or late response are evoked by afferent Aδ and C fibers, respectively. In each case, lower traces are the average transient of 16 responses, upper traces are the rectified integral of averaged signals for quantitative comparison.

2.8 ± 0.4; and for desflurane: RSNA 6.6 ± 1.3, Aδ 3.2 ± 0.6, and C 2.7 ± 0.8.

Spontaneous Renal Sympathetic Nerve Activity

Desflurane. The effect of desflurane was biphasic with an increase in mean activity of 37% at 6% end-tidal concentration ($P < 0.02$), a return to control values at 9%, and subsequent depression of 65.8% at 12% concentration ($P < 0.001$; fig. 3). Recovery occurred within approximately 60 min.

Isoflurane. Changes in RSNA were not statistically significant up to 1.8% ($P > 0.02$; fig. 3), but concentrations of 2.4% caused significant reduction in mean activity to 52.7 ± 22.8% of control ($P < 0.01$). Recovery occurred approximately 30 min after withdrawal of the agent.

Halothane. There was no statistically significant change in mean RSNA up to 1.6% end-tidal concentration (fig. 3).

Somatosympathetic Reflexes

Desflurane. There was no significant change in evoked somatosympathetic responses up to 9% desflurane, but a concentration of 12% caused significant depression of mean Aδ and C reflexes to 34.2 ± 9.2% ($P < 0.01$) and 29.4 ± 11.2% ($P < 0.001$) of control, respectively. Recovery occurred within 30 min (fig. 4).

Isoflurane. Isoflurane produced a concentration-dependent reduction in evoked activity with a greater

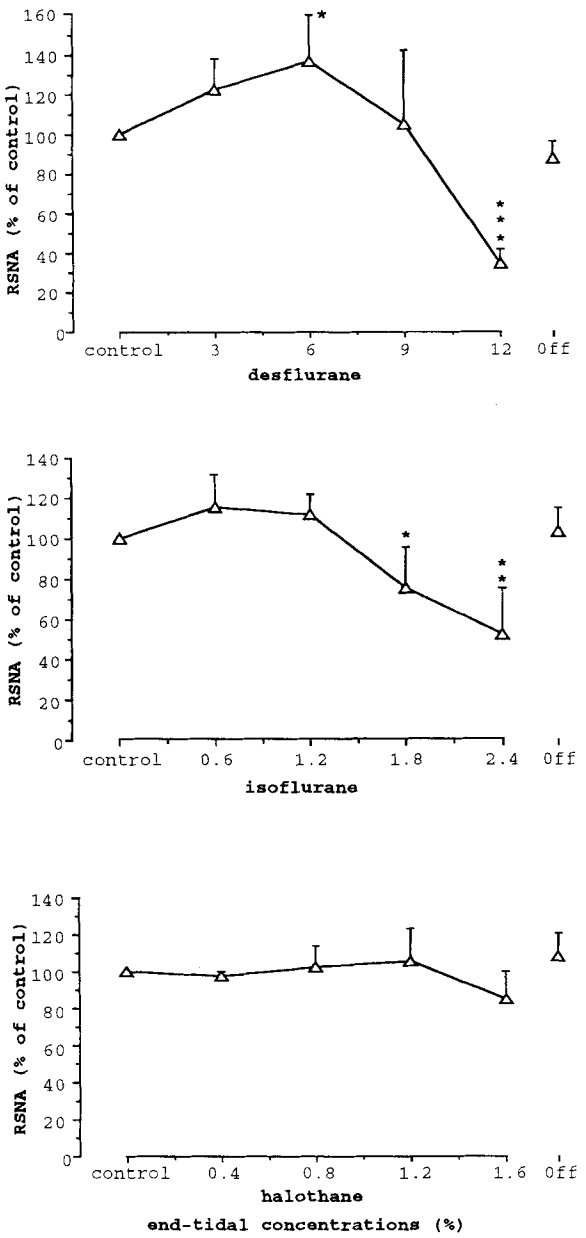

Fig. 3. Concentration–response curves for the effects of increasing end-tidal concentrations of inhalational anesthetics on spontaneous renal sympathetic nerve activity. (*Top*) Desflurane. (*Middle*) Isoflurane. (*Bottom*) Halothane. Values expressed as percentage of control, mean (SD, n = 5) in each group. *Off* indicates values following withdrawal of each agent. Recovery to within control values occurred at 60 min and 30 min for desflurane and isoflurane, respectively. There were no statistically significant changes in response to either the administration or withdrawal of halothane. Asterisks indicate within-group comparison with control: *$P < 0.02$, **$P < 0.01$, ***$P < 0.001$.

effect on C compared with Aδ reflexes (fig. 4). The mean values of the C reflexes were depressed to 70.1% ± 14.1% ($P < 0.01$), 53.2 ± 13.8% ($P < 0.001$), and 27.6 ± 7.8% ($P < 0.001$) of control at end-tidal concentrations of 1.2, 1.8, and 2.4%, respectively, compared with significant depression of Aδ reflexes to only 70.2 ± 9.8% and 50.2%± 11.3% of control at concentrations of 1.8 and 2.4%, respectively ($P < 0.01$). After withdrawal, the mean Aδ reflexes recovered within 20 min, but C reflexes required approximately 60 min. Between 1.2 and 2.4% the greater depression of the C reflexes was significant ($P < 0.02$).

Halothane. Halothane caused a similar concentration dependent depression of both C and Aδ fiber-mediated evoked somatosympathetic reflexes, which returned to control values 60 min after its withdrawal (fig. 4).

Hemodynamics

The control data for observations on the circulation were comparable, and there were neither statistically significant changes in heart rate (table 1) nor significant changes in central venous pressure and pulmonary artery pressure throughout. The mean systemic pressure was reduced by 90 mmHg ($P < 0.01$), 80 mmHg ($P < 0.001$), and 58 mmHg ($P < 0.02$) at concentrations of 12% desflurane, 2.4% isoflurane, and 1.6% halothane, respectively (table 1).

A significant reduction in mean cardiac output of approximately 50% occurred at the highest concentrations of all three agents.

Discussion

An important finding is that isoflurane causes greater depression of C compared with Aδ somatosympathetic reflexes, and also that significant depression of C reflexes lasts considerably longer than for Aδ reflexes, so that effects of isoflurane can be compared with μ-opioids.[11] In contrast, desflurane and halothane cause equal depression of both reflexes, and comparison can be made with κ-opioids,[12] α_2-agonists,[13] and local anesthetics.[14]

Multifiber recordings from renal nerves embody temporal and spatial summation and occlusion of sympathetic neurons and allow averaging to provide quantitative data. Single-fiber studies have sound clinical indications[15] but were rejected for this study because a valid neuronal population survey would require many more animals and complex compilation of data. In anes-

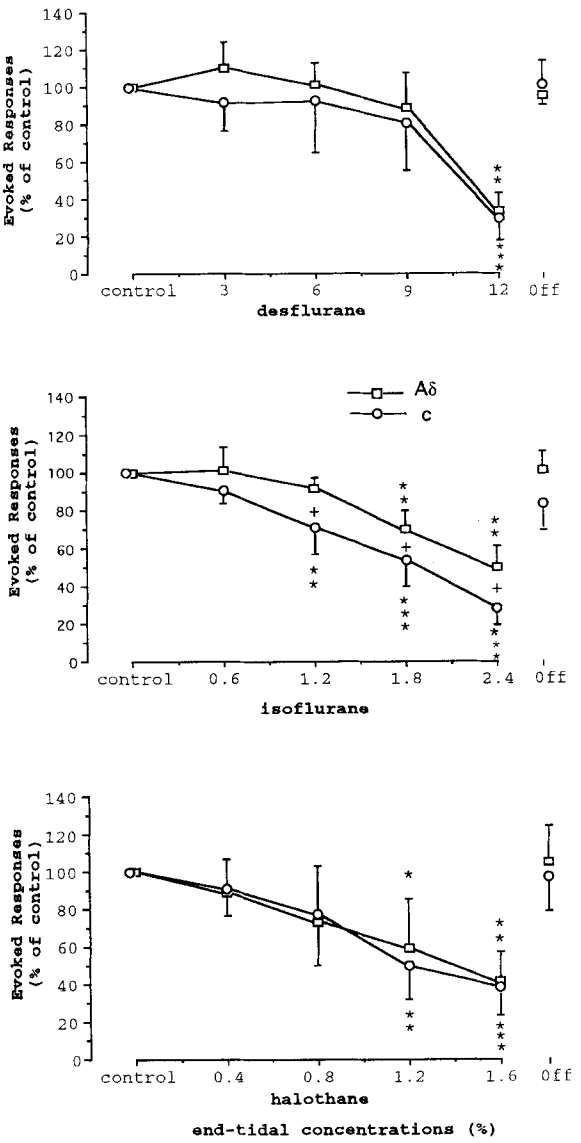

Fig. 4. Effects of increasing expired end-tidal concentrations of inhalational anesthetics on somatosympathetic Aδ (*open squares*) and C (*open circles*) reflexes evoked by supramaximal electrical stimulation of a radial nerve. (*Top*) Desflurane. (*Middle*) Isoflurane. (*Bottom*) Halothane. Data are given as mean (SD, n = 5) in each group. *Off* indicates values following withdrawal of each agent. For desflurane and halothane, recovery of both reflexes occurred at 30 min and 60 min, respectively. In contrast, for isoflurane the mean Aδ response returned to control in 20 min and the mean C reflexes recovered after 60 min. Asterisks indicate comparison of values with control: *$P < 0.02$, **$P < 0.01$, and ***$P < 0.001$. Plus sign indicates comparison between Aδ and C reflexes: +$P < 0.02$.

thetized dogs, a single supramaximal electrical stimulus applied to a mixed peripheral nerve activates all its fibers including C fibers with the highest thresholds. It causes a mass reflex that can be recorded in all efferent sympathetic nerves. After "wind up" of the C reflexes, early and late responses are evoked by small myelinated (group III, Aδ, conduction velocities ≤ 30 m/s) and unmyelinated (group IV, C, conduction velocities ≤ 2.5 m/s) fibers, respectively.[16] Separation of the two responses depends on the length of the afferent pathway and on appropriate placement of the stimulating electrode. Also, for return of the sympathetic neurons to normal excitability between stimuli, the maximal stimulating frequency is normally in the range of 0.2–0.5 Hz and was determined to be 0.33 Hz for the present experimental study protocol.

A rapid increase in the inspired concentration of desflurane causes a transient increase in sympathetic activity, and several groups have concluded that this is a reflex caused by stimulation of both pulmonary and extrapulmonary receptors but do not exclude the possibility of central effects.[15,17,18] However, the present study shows that when desflurane is allowed to equilibrate for periods of 20 min it has a biphasic effect on RSNA, causing a mean increase of approximately 37% up to 6% concentration, followed by depression of approximately 66% at 12% concentration. This study also shows dissociation between the effect of halothane on somatosympathetic reflexes, which it depresses, and resting RSNA, on which it had no significant effect. Such dissociation is also true for desflurane, which at relatively low concentrations causes excitation of RSNA without any significant effect on somatosympathetic reflexes.

For isoflurane the ED_{50}s for Aδ and C reflexes were 2.4% and 1.9%, respectively; for desflurane and halothane, which had equal effects on both Aδ and C reflexes, they were approximately 11% and 1.4%, respectively. Allowing for higher minimum alveolar concentrations (MACs) in dogs, these are similar to the ED_{100}s for MAC required to block the adrenergic response in humans.[3,4] Also, concentrations of desflurane as high as 1.66 MAC are required to suppress nociceptive cardiovascular responses.[19]

Although the hemodynamic data reported here are compatible with previous studies,[20,21] there are conflicting reports on the effects of halothane on sympathetic activity.[23–26] In cats anesthetized with nitrous oxide in oxygen, halothane was reported to reduce both sympathetic nerve activity and blood pressure.[20,25] However, in another study in cats anesthetized with halothane

Table 1. Effects of Inhalational Anesthetic Agents on Hemodynamic Variables in Dogs

		End-tidal Concentrations				
Desflurane	Control	3%	6%	9%	12%	Recovery
HR	138 (25)	154 (33)	155 (19)	144 (11)	126 (10)	146 (27)
MAP	140 (15)	141 (22)	128 (18)	103 (22)*	50 (14)†	145 (15)
CO	2.42 (0.82)	2.10 (0.55)	2.33 (0.68)	2.20 (0.72)	1.22 (0.40)*	2.10 (0.54)
Isoflurane	Control	0.6%	1.2%	1.8%	2.4%	Recovery
HR	139 (17)	138 (23)	141 (12)	134 (13)	123 (8)	139 (11)
MAP	149 (5)	143 (6)	128 (4)*	95 (16)*	69 (11)†	145 (4)
CO	2.62 (0.36)	2.59 (0.76)	2.57 (0.66)	1.93 (0.48)	1.34 (0.33)†	2.27 (0.52)
Halothane	Control	0.4%	0.8%	1.2%	1.6%	Recovery
HR	136 (30)	141 (36)	144 (20)	140 (25)	135 (14)	136 (19)
MAP	140 (21)	129 (24)	110 (26)	94 (33)*	82 (28)*	130 (13)
CO	2.53 (0.42)	2.41 (0.71)	2.35 (0.59)	2.08 (0.49)	1.37 (0.33)†	2.22 (0.72)

Data are mean (SD) (n = 5).

HR = heart rate (bpm); MAP = mean arterial pressure (mmHg); CO = cardiac output (l/min).

* $P < 0.01$, † $P < 0.001$: mean values compared with control.

RSNA increased during hypotension, which could indicate compensation by partially depressed baroreflexes, which was also true in another study in dogs.[26] The effects of isoflurane and desflurane on baroreflex sensitivity at concentrations greater than 0.5 MAC have been reported to be similar.[27] The observation that desflurane, unlike isoflurane, has a biphasic effect on mean RSNA provides evidence that although its excitatory phase[15] is regarded as being largely caused by pulmonary and extrapulmonary reflexes,[17,18] a decrease in arterial pressure acting through the baroreflexes cannot be excluded as a contributory factor.

There are many reviews relevant to the central organization of the regulation of the sympathetic and cardiovascular systems.[28,29] Until relatively recently the role of the spinal cord has not been a major consideration in the mechanism of inhalational anesthesia, in spite of a considerable body of evidence showing that inhalational anesthetics affect sensory processing in the dorsal horn,[30-33] which may be laminar-specific.[33] Also, the MAC values of inhalational agents are highly dependent on their effects on the spinal cord,[34,35] and synergistic interaction has been shown to occur between the effects of sevoflurane and intrathecal fentanyl.[36]

Modern reviews suggest that inhalational anesthetics in adequate concentrations modify every aspect of cellular function that has so far been studied, and that several functions may be affected simultaneously.[37,38] However, current opinion is that interaction with proteins and ion channels is important to mechanisms of inhalational anesthesia.[40,41] Also, both inhibitory and excitatory neurotransmitters are involved in the actions of inhalational anesthetic drugs in the nervous system.[42,43] Hitherto, the landmarks for the effects of increasing concentrations of inhalational anesthetics have involved single end points including hypnosis,[44] (ED_{100}) MAC[1,39] (ED_{100} in 50% of a study group) and MAC required to block the adrenergic response[3,4] (ED_{100} for abolition of adrenergic responses to surgical stimulation).[39,44] It is not possible to study the ED_{100}s for abolition of sympathetic activity without perfusion techniques. However, at the higher concentrations in the present study, isoflurane had a greater effect on C compared with Aδ reflexes, which has also been reported for sevoflurane.[9] In neither of these two cases can this be related to lipid solubility, because desflurane and halothane had equal effects on both reflexes. Arguably such specificity of effect may provide further evidence supporting the role of protein chemistry in the mechanisms of anesthesia.

In summary, the greater effect of isoflurane on C compared with Aδ reflexes does not occur with desflurane and halothane and hence is not correlated with their lipid solubilities. A dissociation was observed between spontaneous and evoked sympathetic activity during the administration of halothane and also at low concentrations of desflurane. The concentrations required to produce 50% depression of somatosympathetic reflexes are greater than those required to induce hypnosis and MAC

and are similar to MAC required to block the adrenergic response.

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