Respiratory reflexes in spontaneously breathing anesthetized dogs in response to nasal administration of sevoflurane, isoflurane, or halothane

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Objective—To characterize respiratory reflexes elicited by nasal administration of sevoflurane (Sevo), isoflurane (Iso), or halothane (Hal) in anesthetized dogs.

Animals—8 healthy Beagles.

Procedure—A permanent tracheostomy was created in each dog. Two to 3 weeks later, dogs were anesthetized by IV administration of thiopental and α-chloralose. Nasal passages were isolated such that inhalant anesthetics could be administered to the nasal passages while the dogs were breathing 100% O_2 via the tracheostomy. Respiratory reflexes in response to administration of each anesthetic at 1.2 and 2.4 times the minimum alveolar concentration (MAC) and the full vaporizer setting (5%) were recorded. Reflexes in response to administration of 5% of each anesthetic also were recorded following administration of lidocaine to the nasal passages.

Results—Nasal administration of Sevo, Iso, and Hal induced an immediate ventilatory response characterized by a dose-dependent increase in expiratory time and a resulting decrease in expired volume per unit of time. All anesthetics had a significant effect, but for Sevo, the changes were smaller in magnitude. Responses to administration of each anesthetic were attenuated by administration of lidocaine to the nasal passages.

Conclusions and Clinical Relevance—Nasal administration of Sevo at concentrations generally used for mask induction of anesthesia induced milder reflex inhibition of breathing, presumably via afferent neurons in the nasal passages, than that of Iso or Hal. Respiratory reflexes attributable to stimulation of the nasal passages may contribute to speed of onset and could promote a smoother induction with Sevo, compared with Iso or Hal. (*Am J Vet Res* 2001;62: 311–319)

Induction of anesthesia with inhalation anesthetics is sometimes associated with airway reflexes such as apnea, breath-holding, laryngospasm, and hypersecretion[1-3] as well as exaggerated responses to excitement.[2,4] These undesirable responses are believed to be the result of irritation of the mucosa of the nasal passages, pharynx, and larynx, which may impair smooth induction of anesthesia and lead to airway obstruction and associated hypoxia and hypercapnia in dogs,[2-4] cats,[5] rabbits,[6,7] and humans.[8-10] The degree of airway irritation varies with the type of inhalant and its concentration.[11] **Isoflurane (Iso)** has a high rate of complications during induction of anesthesia in humans.[8] **Halothane (Hal)** reportedly is slightly less irritating to airways than Iso, but it causes similar reflex reactions when inhaled at concentrations used for induction of anesthesia in humans.[9-11] In contrast, **sevoflurane (Sevo)**, a halogenated volatile anesthetic with a lower blood-gas partition coefficient (0.65 at 37 C) than that of other anesthetics (ie, 1.40 for Iso; 2.30 for Hal), produces less airway irritation and provides a rapid and smooth onset of anesthesia when mask induction is used.[8-10] We have reported[12,a] that Sevo administered locally into the functionally isolated airway, including the portion of the respiratory tract from the nasal passages to the larynx, while dogs are breathing via a tracheostomy produces less ventilatory depression and shorter induction time than is evident for similar administration of Iso and Hal in anesthetized, spontaneously breathing dogs.

In the respiratory tract, the nasal passages are particularly rich in sensory afferent nerves[13] that elicit various respiratory reflexes such as apnea, sneezing, laryngeal closure, bronchoconstriction, and hypersecretion of mucus in response to various chemical and mechanical irritants.[14] In several studies, it has been proposed that the nasal passages are vulnerable to inhalation anesthetics. Clinically, use of a mask to induce anesthesia with Sevo is faster in humans when the drug is administered through the mouth instead of through the nose; moreover, this method encourages fewer changes in breathing patterns.[15] Regarding the respiratory reflexes in response to inhalation anesthetics administered into the nasal passages, Nishino et al[16] reported that topical nasal insufflation of 5% Hal and Iso changed the breathing pattern of anesthetized humans. In a recent study, Mutoh et al[17] documented that Hal administered into the nasal passages induced a dose-dependent ventilatory depression characterized by prolongation of expiration time and a decrease in tidal volume in anesthetized, spontaneously breathing dogs. Furthermore, Mutoh et al[17] proposed that stimulation of sensory receptors located in the nasal mucosa plays a major

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role in eliciting these responses via afferent fibers of the trigeminal nerve.

When all this information is taken into consideration, it is presumed that immediate ventilatory depression can be provoked by local administration of inhalation anesthetics into the nasal passages, which may limit rapid and smooth onset of induction with inhalants administered via a mask. However, there is little understanding of the respiratory reflexes in response to nasal administration of newer inhalation anesthetics currently used in veterinary practice. Therefore, the objective of the study reported here was to determine respiratory reflexes in dogs in response to nasal administration of Sevo, Iso, or Hal. We used the same experimental procedure reported elsewhere,[17] thereby ensuring that respiratory reflexes for the nasal passages during administration of inhalation anesthetics were investigated in anesthetized, spontaneously breathing dogs.

Materials and Methods

Animals—Eight Beagles (4 females and 4 males) were used. Dogs ranged from 10 to 16 months old (mean, 13.5 months), and body weight ranged from 8.3 to 10.5 kg (mean, 9.5 kg). Dogs were housed separately in runs maintained at constant temperature and humidity. Dogs were fed a commercial dry food once daily; water was available ad libitum. Food was withheld for the 12-hour period preceding initiation of the experiments. All experimental procedures were reviewed and approved by the Animal Care Committee of the Graduate School of Agricultural and Life Sciences and were performed in accordance with the *NIH Guide for the Care and Use of Laboratory Animals* and the *Guidelines for Animal Experimentation* established by the Japanese Association for Laboratory Animal Science.

Animal preparation—Two to 3 weeks before the study, each dog underwent surgery to create a permanent tracheostomy, as described elsewhere.[17-19] Briefly, dogs were anesthetized with Sevo and positioned in dorsal recumbency. The skin of the tracheal area was incised on the ventral midline, the sternohyoideus muscles were separated, and the ventral aspect of the trachea was exposed. Medial edges of the sternohyoideus muscles were sutured together dorsal to the trachea to elevate the trachea to the skin; surgeons were careful to avoid damaging the recurrent laryngeal nerves. Ventral sections of 3 tracheal rings midway between the cricoid cartilage and the thorax were removed, but the tracheal mucosa was left intact. Mucosa then was dissected to create a margin of approximately 5 mm; skin was sutured to the tracheal mucosa with

Table 1—Respiratory and cardiovascular variables associated with nasal administration of sevoflurane (Sevo), isoflurane (Iso), and halothane (Hal) at 1.2 and 2.4 times the minimum alveolar concentration (MAC) to 8 spontaneously breathing anesthetized dogs

		1.2 MAC		2.4 MAC	
Variable	Anesthetic	Baseline	Peak response	Baseline	Peak response
T_I (s)					
	Sevo	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.2
	Iso	1.2 ± 0.1	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.2
	Hal	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
T_E (s)					
	Sevo	3.0 ± 0.2	3.0 ± 0.2	3.2 ± 0.2	4.0 ± 0.2*
	Iso	2.9 ± 0.2	3.1 ± 0.1	3.1 ± 0.2	5.7 ± 0.4*†
	Hal	3.0 ± 0.2	3.1 ± 0.2	3.2 ± 0.2	5.1 ± 0.5*†
f_R (breaths/min)					
	Sevo	14 ± 1	14 ± 1	13 ± 1	12 ± 1*
	Iso	15 ± 2	16 ± 2	14 ± 1	9 ± 2*†
	Hal	14 ± 1	14 ± 2	14 ± 1	10 ± 1*†
V_T (ml)					
	Sevo	195 ± 13	192 ± 11	198 ± 8	198 ± 10
	Iso	188 ± 10	183 ± 13	193 ± 10	189 ± 14
	Hal	190 ± 9	184 ± 11	196 ± 11	194 ± 15
$\dot{V}_E$(L/min)					
	Sevo	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.3 ± 0.1*
	Iso	2.6 ± 0.1	2.6 ± 0.2	2.7 ± 0.1	1.8 ± 0.2*†
	Hal	2.6 ± 0.2	2.7 ± 0.2	2.6 ± 0.2	2.0 ± 0.2*†
P_{ETCO_2} (mm Hg)					
	Sevo	39 ± 1	41 ± 2	40 ± 1	41 ± 1
	Iso	40 ± 1	41 ± 1	39 ± 1	45 ± 2*†
	Hal	40 ± 1	40 ± 2	40 ± 1	43 ± 2*†
HR (beats/min)					
	Sevo	105 ± 7	107 ± 7	107 ± 7	107 ± 6
	Iso	106 ± 7	106 ± 7	107 ± 6	107 ± 8
	Hal	106 ± 9	106 ± 8	107 ± 7	108 ± 8
MAP (mm Hg)					
	Sevo	97 ± 7	98 ± 8	94 ± 7	94 ± 9
	Iso	96 ± 8	97 ± 8	92 ± 7	91 ± 8
	Hal	97 ± 7	97 ± 8	92 ± 9	92 ± 8

Data are reported as mean ± SEM.

*Value is significantly ($P < 0.05$) different from baseline value. †Value is significantly ($P < 0.05$) different from value obtained after administration of each anesthetic at 1.2 MAC.

T_I = Inspiration time. T_E = Expiration time. f_R = Respiratory frequency. V_T = Tidal volume. $\dot{V}_E$ = Expired volume per unit time. P_{ETCO_2} = End-tidal PCO_2. HR = Heart rate. MAP = Mean arterial blood pressure.

polypropylene monofilament suture (No. 3 to 0). Butorphanol (0.4 mg/kg of body weight) was administered IM prior to the end of the anesthetic episode and subsequently every 6 hours for 24 hours. During the adjustment period after surgery, the tracheostomy site was carefully cleaned and nebulized with saline (0.9% NaCl) solution when necessary. Dogs were given cefazolin (15 mg/kg, PO, q 12 h for 10 days) after surgery. Blood samples were obtained every day and submitted for CBC and serum biochemical analyses.

Procedures—For the experiments in the study, dogs were sedated with a combination of an opioid and tranquilizer and anesthetized with a combination of a thiobarbiturate and α-chloralose.[20] On the day of each experiment, dogs were medicated with a mixture of acepromazine (0.05 mg/kg) and buprenorphine (0.01 mg/kg) administered IV through a catheter inserted in a cephalic vein. Anesthesia was induced with thiopental (1.5 to 5.0 mg/kg, IV), a cuffed tracheostomy tube[b] was inserted, and α-chloralose (50 mg/kg, IV) was injected slowly during a period of 15 to 20 minutes. All dogs were allowed to breathe spontaneously; 100% O_2 was delivered via the tracheostomy tube at a flow rate of 3 L/min, using a semiclosed circle anesthesia system.[c] Anesthesia was maintained by use of α-chloralose (5 mg/kg per h, IV) administered by an infusion pump. Adequacy of anesthesia was assessed by determining responses to application of a tail clamp[20] 10 to 15 minutes before surgical intervention and before each experimental episode and by determining responses to pinching the interdigital skin of a hind limb every 30 minutes.[17,19] When a positive response (eg, limb twitch or withdrawal or a sudden fluctuation in mean arterial blood pressure [> 5 mm Hg] or heart rate [> 10%]) was observed, a supplemental dose of thiopental (0.5 mg/kg, IV) was given slowly, and the procedure was repeated until an adequate anesthetic depth was obtained. In preliminary studies, dogs anesthetized in this manner did not have any

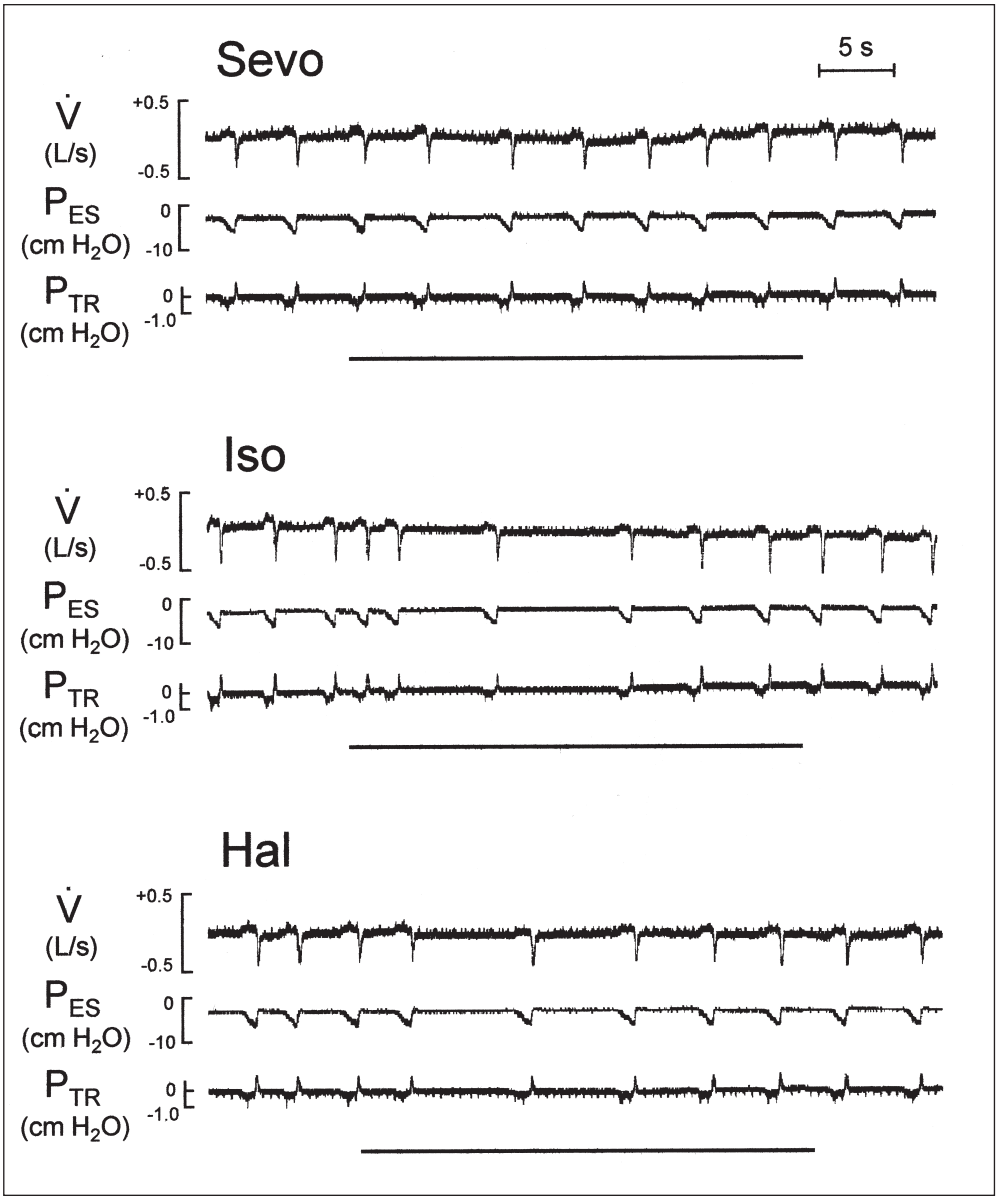

Figure 1—Recordings illustrating respiratory reflexes in response to nasal administration of 2.4 times the minimum alveolar concentration (MAC) of sevoflurane (Sevo), isoflurane (Iso), and halothane (Hal) for 30 seconds in a spontaneously breathing anesthetized dog. $\dot{V}$ = Respiratory airflow. P_{ES} = Esophageal pressure. P_{TR} = Intratracheal pressure.

changes in breathing patterns or blood gas tensions for at least 200 minutes. However, injection of additional thiopental sometimes caused apnea. Therefore, during the study reported here, sufficient time (3 to 5 minutes) was allowed to elapse after administration of thiopental to allow the dogs to resume a constant breathing pattern. Total cumulative doses (mean ± SD) of thiopental and α-chloralose administered were 5.0 ± 1.2 and 67.5 ± 2.5 mg/kg, respectively. Total duration of anesthesia was 208 ± 16 minutes.

After anesthesia was induced, dogs were positioned in dorsal recumbency. Respiratory airflow was measured with a differential pressure transducer[d] through 2 sidearms connected to the tracheostomy tube. Airflow was integrated with an A-D converter[e] connected to a personal computer, which calculated the **tidal volume (V_T)**. **Expired volume per unit time** ($\dot{V}_E$) was calculated from V_T and the total cycle duration. A cuffed nasopharyngeal cannula (ID, 4.5 to 5.0 mm) was introduced into the nasopharynx through the tracheostomy, and a nasal cannula with a pair of cuffed tubes was inserted into the nostrils to functionally isolate the nasal cavity. A polyethylene catheter (ID, 2 mm) filled with saline solution was placed in the middle portion of the esophagus and connected to a pressure transducer[f] to record the esophageal pressure. **Inspiration time (T_I)** and **expiration time (T_E)** were measured from tracings of esophageal pressure. **Respiratory frequency (f_R)** was calculated from T_I and T_E. Arterial blood pressure was monitored with a pressure transducer[f] connected to a 20-gauge catheter inserted in a femoral artery. All signals were displayed on a thermal-array recorder[g] and recorded on magnetic tape.[h] Samples of tidal gases were obtained by use of a tube connected to the tip of the tracheostomy tube, and **end-tidal P_{CO_2} (P_{ETCO_2})** was measured by use of a gas analyzer.[i] Lactated Ringer solution was infused at a rate of 10 ml/kg/h through the catheter inserted in the cephalic vein. Rectal temperature (mean ± SD) was maintained at 37 ± 1 C by use of a warming blanket.

After preparations were completed, 15 minutes were allowed to elapse so that dogs would attain a stable stage of anesthesia and cardiopulmonary function. At the commencement of each experiment, P_{ETCO_2} was maintained between 38 and 42 mm Hg. The P_{ETCO_2} values were adjusted by use of manual lung inflations delivered in a typical manner (ie, squeezing the rebreathing bag with the pop-off valve closed) when necessary. In this study, manual ventilation was performed in all dogs after nasal administration of 5% Iso or Hal. The P_{ETCO_2} was returned to the reference range within 15 to 45 seconds after starting the ventilatory assistance, and dogs were gradually weaned from manual to spontaneous ventilation by synchronizing the frequency (12 to 16 breaths/min) with each dog's spontaneous respiratory cycle. Arterial blood samples then were collected in heparinized syringes. Blood pH, P_{aO_2}, and P_{aCO_2} were measured, using a blood-gas analyzer.[j] The subsequent experiment was performed when pH, P_{aO_2}, and P_{aCO_2} were within reference ranges.

Determination of respiratory reflexes—Oxygen (100%) was administered through the nasal cannula at a rate of 5 L/min until respiratory cycles and intranasal temperature were constant for a period of ≥ 1 minute. Sevoflurane, Iso, or Hal then was administered through the nasal cannula at concentrations of 1.2 and 2.4 times the **minimum alveolar concentration (MAC)** and at a concentration with the vaporizer fully open (5%). The MAC values for Sevo, Iso, and Hal were 2.09, 1.30, and 0.94%, respectively.[21] Thus, 5% was the maximum dose of Sevo (2.4 MAC) to which dogs were exposed, whereas 5% represented 3.8 MAC for Iso and 5.3 MAC for Hal. The maximum concentration in this study was 5%, because our vaporizers for Sevo had a maximum concentration of 5% on the dial, and that is the concentration we have typically used for mask or chamber induction. Order of

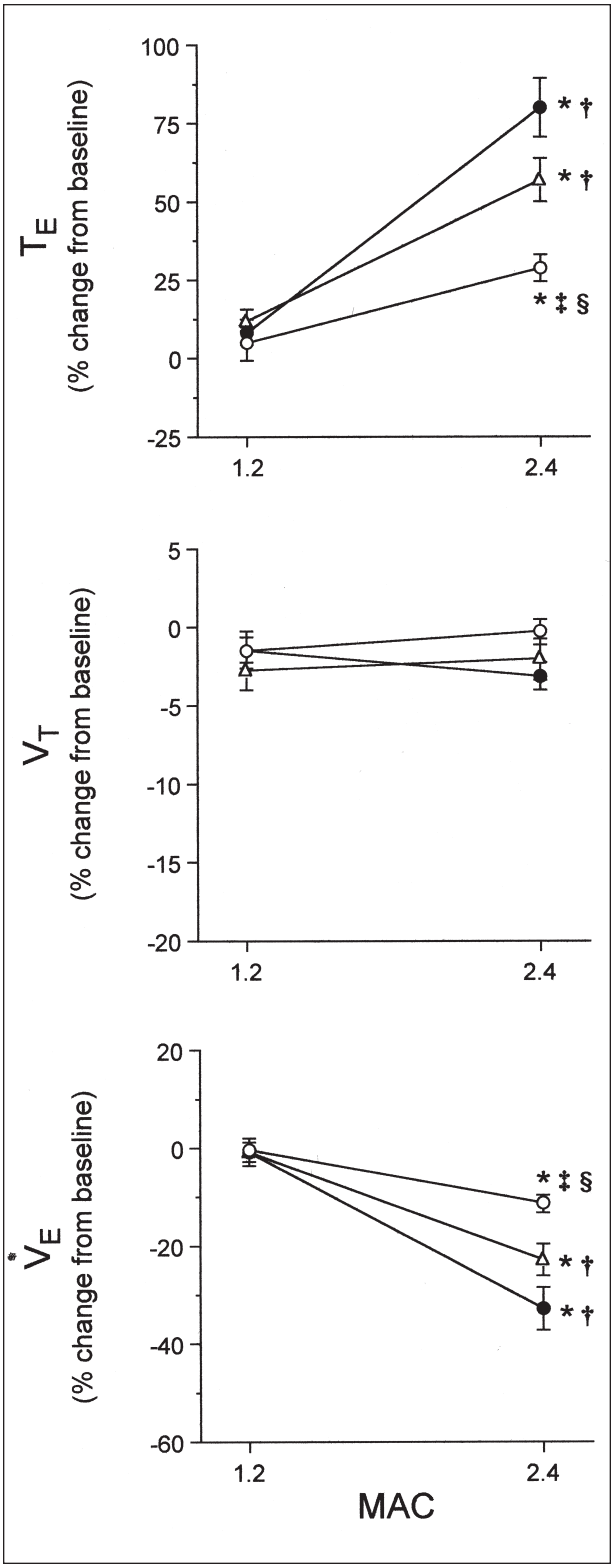

Figure 2—Changes in mean ± SEM expiratory time (T_E), tidal volume (V_T), and expired volume per unit time ($\dot{V}_E$) in response to nasal administration of Sevo (●), Iso (○), and Hal (Δ) in anesthetized dogs. *Value is significantly ($P < 0.05$) different from baseline value. †Value is significantly ($P < 0.05$) different from value obtained after administration of each anesthetic at 1.2 MAC. ‡Value is significantly ($P < 0.05$) different from value obtained after administration of Iso. §Value is significantly ($P < 0.05$) different from value obtained after administration of Hal.

administration (anesthetics and concentrations) was randomized, and each anesthetic was administered at each concentration for 30 seconds, with an interval of 10 minutes before administration of the next concentration. Each anesthetic also was administered at a concentration of 2.4 MAC (n = 4) or 5% (4) for up to 3 minutes to evaluate the effects of prolonged exposure.

For administration of anesthetics through the nasal cannula, a semiclosed circle anesthesia system[c] with the vaporizer[k-m] outside the circle was used. The anesthetic vaporizer that was used was specifically calibrated for use with each anesthetic and had a vaporizer setting for each intended anesthetic concentration. Anesthetic concentration in the nasal passages was measured by collecting gas samples from

Table 2—Respiratory and cardiovascular variables associated with nasal administration of Sevo, Iso, and Hal at 5% (vaporizer fully open) to 8 spontaneously breathing anesthetized dogs before and after administration of lidocaine to the nasal passage

		Before lidocaine		After lidocaine	
Variable	Anesthetic	Baseline	Peak response	Baseline	Peak response
T_I (s)					
	Sevo	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.1
	Iso	1.3 ± 0.1	1.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.1
	Hal	1.3 ± 0.1	1.4 ± 0.2	1.3 ± 0.1	1.3 ± 0.1
T_E (s)					
	Sevo	3.2 ± 0.2	4.2 ± 0.3*†	3.5 ± 0.2	3.4 ± 0.2§
	Iso	3.3 ± 0.1	6.2 ± 0.4*†‡	3.4 ± 0.2	3.5 ± 0.2§
	Hal	3.4 ± 0.2	8.3 ± 0.7*†‡	3.5 ± 0.2	3.7 ± 0.3§
f_R (breaths/min)					
	Sevo	13 ± 1	11 ± 1*‡§	13 ± 2	13 ± 1§
	Iso	12 ± 1	8 ± 3*†	12 ± 2	12 ± 2§
	Hal	12 ± 1	5 ± 3*†‡	13 ± 1	12 ± 2§
V_T (ml)					
	Sevo	202 ± 8	195 ± 10§	195 ± 13	192 ± 11
	Iso	198 ± 10	193 ± 9	188 ± 10	183 ± 13
	Hal	208 ± 11	183 ± 12*†	190 ± 9	184 ± 11§
$\dot{V}_E$ (L/min)					
	Sevo	2.6 ± 0.2	2.3 ± 0.2*†	2.7 ± 0.2	2.7 ± 0.2§
	Iso	2.7 ± 0.2	1.6 ± 0.3*†‡	2.8 ± 0.1	2.8 ± 0.2§
	Hal	2.6 ± 0.2	0.9 ± 0.3*†‡	2.7 ± 0.1	2.8 ± 0.2§
$PETCO_2$ (mm Hg)					
	Sevo	40 ± 1	42 ± 1	39 ± 1	38 ± 1
	Iso	39 ± 1	44 ± 2*†	40 ± 1	41 ± 1§
	Hal	40 ± 1	47 ± 2*†‡	40 ± 1	40 ± 2§
HR (beats/min)					
	Sevo	102 ± 6	102 ± 5	100 ± 8	99 ± 8
	Iso	103 ± 6	102 ± 7	99 ± 7	100 ± 8
	Hal	102 ± 7	101 ± 7	100 ± 7	100 ± 7
MAP (mm Hg)					
	Sevo	96 ± 7	97 ± 7	94 ± 7	93 ± 8
	Iso	98 ± 7	98 ± 8	92 ± 8	93 ± 8
	Hal	99 ± 9	97 ± 8	92 ± 7	91 ± 8

Data are reported as mean ± SEM.
‡Value is significantly ($P < 0.05$) different from value obtained for administration of each anesthetic at 2.4 MAC. §Value is significantly ($P < 0.05$) different from value obtained for administration of each anesthetic at 5% before administration of lidocaine.
See Table 1 for remainder of key.

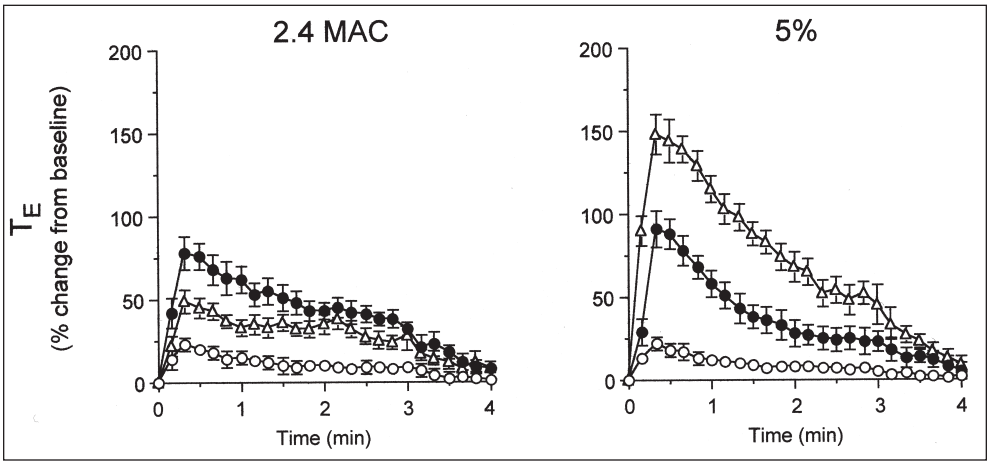

Figure 3—Effects of nasal administration of 2.4 MAC (left) and 5% (right) Sevo, Iso, and Hal for 3 minutes on mean ± SEM T_E in dogs (n = 4 dogs/concentration). *See* Figure 2 for key.

a sample tube connected to the distal end of the nasopharyngeal cannula and measuring the concentration with an infrared gas analyzer.[n] Data were simultaneously downloaded to a personal computer, and anesthetic concentration was calculated every 5 seconds.

Effects of local anesthesia on respiratory reflexes—After completion of the dose-response study, respiratory responses to administration of 5% Sevo, Iso, or Hal (with or without prior local anesthesia) were determined in all anesthetized, spontaneously breathing dogs. Reflex responses to administration of each anesthetic at a concentration of 5% were used as control responses, because qualitatively similar respiratory reflexes were elicited by each anesthetic at any concentration, and the most dramatic evoked responses were observed at the highest concentrations. To administer lidocaine to the nasal passages, 5 ml of a 2% solution of lidocaine[o] was aerosolized with an ultrasonic nebulizer[p] driven by the O_2 (5 L/min; output, 2.5 ml/min), producing particles that were approximately 5 µm in diameter. The aerosol was administered via the nasal cannula for 2 minutes. The nebulizer then was turned off, and respiratory reflexes in response to administration of 5% halothane were measured for 30 seconds.

At the end of the experiments, dogs were euthanatized by administration of an overdose of pentobarbital (50 mg/kg, IV). Dogs were necropsied within 1 hour after death to evaluate histologic changes in the trachea caused by permanent tracheostomy. The entire trachea, including the tracheostomy site, was removed and sectioned into thin round slices at 1-cm intervals from the tracheostomy site to the larynx. Sections were preserved in formalin, processed, and evaluated histologically. Squamous metaplasia or loss of the epithelium was observed circumferentially surrounding the tracheostomy site and extending 2.8 ± 0.4 (mean ± SD) cm from the site; however, histologic changes were not observed in the laryngeal mucosa.

Data analysis—Respiratory variables (T_I, T_E, f_R, V_T, $\dot{V}_E$, and P_{ETCO_2}) were analyzed on a breath-by-breath basis. Baseline values for respiratory variables were obtained by determining the mean of values for 3 consecutive breaths immediately before each experiment. **Mean arterial blood pressure (MAP)** was calculated every 5 seconds and was the sum of diastolic pressure plus a third of the pulse pressure. **Heart rate (HR)** was derived electrophysiologically from the blood pressure signal. Baseline values for cardiovascular variables were obtained by determining the mean of values for 1 minute before each experiment. Experimental values were peak responses recorded after the onset of each anesthetic administration.

For comparisons of differences between baseline values for each experiment, a 1-way ANOVA was used. To determine whether the changes from baseline to experimental values within each experiment differed significantly, a paired Student *t*-test was used. Evoked changes (Δ) from baseline values in each anesthetic group were compared among treatments and dogs, using a 2-way ANOVA. When the interaction was significant, the Tukey post hoc test was used. For comparisons of evoked changes among anesthetic groups, a 1-way ANOVA followed by the Tukey test was used. Values of $P < 0.05$ were considered significant. Data were expressed as mean ± SEM, unless otherwise indicated.

Results

Respiratory variables in response to nasal administration of Sevo, Iso, or Hal—Baseline values of respiratory variables were not significantly different among experiments (**Table 1**). Nasal administration of Sevo, Iso, or Hal for 30 seconds produced an inhibition of breathing characterized by a dose-dependent increase in T_E and a resultant decrease in $\dot{V}_E$ (**Fig 1**). A significant decrease in V_T was observed in response to

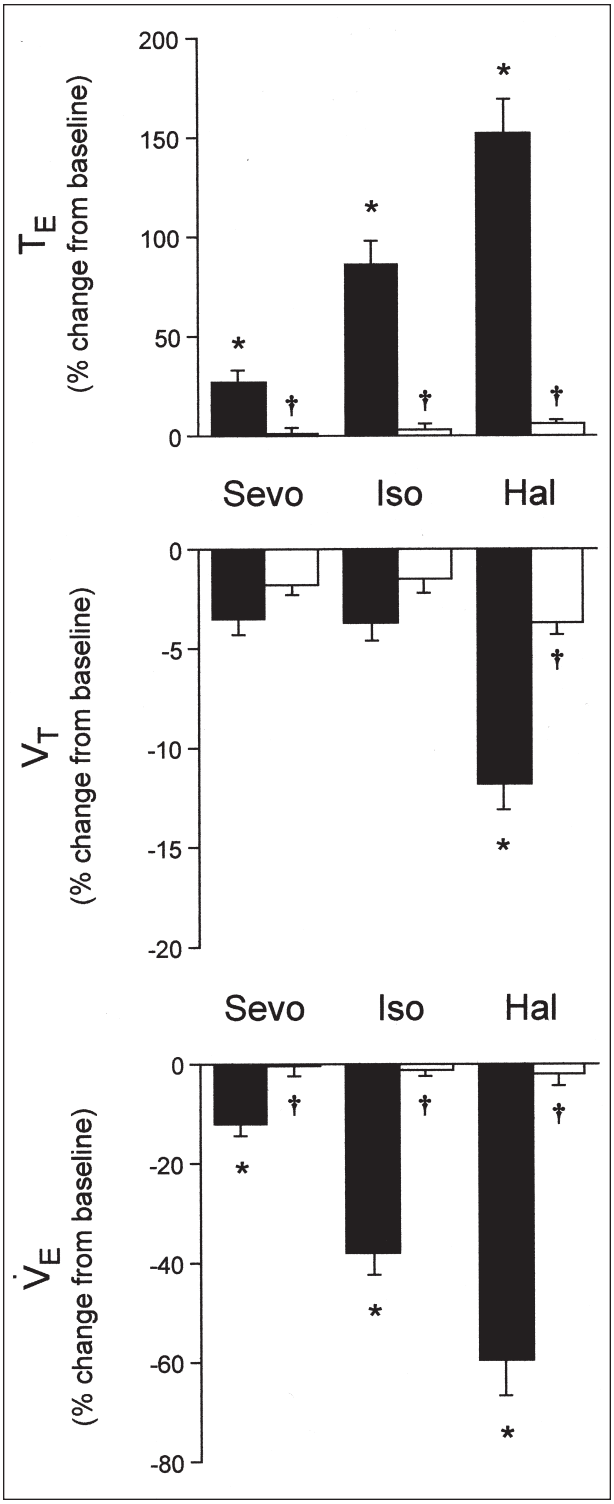

Figure 4—Changes in mean ± SEM T_E, V_T, and V_E in response to nasal administration of 5% Sevo, Iso, and Hal in dogs before (■) and after (□) anesthesia of the nasal passages accomplished by administration of lidocaine. *Value is significantly ($P < 0.05$) different from baseline value. †Value is significantly ($P < 0.05$) different from responses to each anesthetic before administration of lidocaine to nasal passages.

nasal administration of 5% Iso or Hal (**Table 2**). A significant increase in P_{ETCO_2} was detected during administration of Hal or Iso at concentrations of 2.4 MAC and 5%. Respiratory reflexes in response to nasal administration of Sevo at concentrations of 5% were significantly smaller than those of Hal and Iso (**Fig 2**). Although Hal and Iso produced similar responses at 2.4 MAC, 5% Hal had the greatest effect on reflexes in response to nasal administration. Peak responses were detected at 5% in all dogs after 18.2 ± 2.4 seconds for administration of Sevo, 16.0 ± 2.1 seconds for Iso, and 14.6 ± 2.8 seconds for Hal. Time required to achieve a peak response was not significantly different among the anesthetic groups.

Values of T_I, HR, and MAP did not change significantly in any experiment during the study (Tables 1 and 2).

Effects of prolonged exposure to nasal administration of Sevo, Iso, or Hal—When 2.4 MAC and 5% Sevo, Iso, or Hal were administered for 3 minutes, T_E began to increase immediately (**Fig 3**). Peak responses were detected 17.7 ± 2.5, 15.6 ± 2.4, and 14.5 ± 3.0 seconds after the onset of administration of Sevo, Iso, and Hal, respectively. Thereafter, the effect began to wane but lasted until cessation of administration. Peak response and time required to achieve a peak response after administration of each anesthetic for 3 minutes and administration for 30 seconds were not significantly different; Sevo induced the smallest time-course changes in T_E response. A significant increase in P_{ETCO_2} was detected during administration of Hal or Iso at concentrations of 2.4 MAC and 5%. Respiratory reflexes in response to nasal administration of Sevo at concentrations of 5% were significantly smaller than those of Hal and Iso (Fig 2).

Effects of local anesthesia on respiratory reflexes in response to nasal administration of Sevo, Iso, or Hal—Respiratory variables were not significantly different before and after lidocaine nebulization into the nasal passages (Table 2). Ventilatory-depressor reflex responses to nasal administration of 5% of each anesthetic were completely abolished following local anesthesia of the nasal passages achieved by administration of lidocaine (**Fig 4**).

Discussion

In the study reported here, ventilatory-depressor responses during administration of inhalation anesthetics into nasal passages were characterized by a dose-dependent increase in T_E and a decrease in V_T. Inhibitory effects on the breathing pattern (apnea) were essentially similar to those observed for the larynx of dogs, with Hal and Iso decreasing $\dot{V}_E$ as a result of decreases in frequency and V_T.[12,14] In addition to changes in breathing pattern, we consistently found an increase in P_{ETCO_2} after administration of Hal and Iso into the nasal passages. The overall respiratory reflex response to inhalants from the nasal passages differs from that evoked in the tracheobronchial tree and lungs. Brief inhalation of Hal, Iso, or Sevo into the tracheobronchial tree and lungs via a tracheostomy induces tachypnea (increased frequency and decreased V_T) in dogs, the degree of which is greater with Hal or Iso than with Sevo.[22] It is still unclear how these effects clinically interact with ventilation during induction achieved by use of a mask; however, reflex inhibition of breathing that arose from stimulation of the nasal mucosa plays a potential role in triggering respiratory impairment during the early phase of mask induction in dogs.

Adverse effects of halogenated volatile anesthetics during mask induction are characterized by apnea, breath-holding, coughing, laryngospasm, bronchoconstriction, secretion, or excessive body movements.[1-3] In the study reported here, we did not detect a powerful defense reaction such as coughing or sneezing that is commonly observed in humans, even though the most potent anesthetic (5% Hal; equivalent to 5.3 MAC) was administered. This may be attributable to the fact that the dogs already were anesthetized, and, thus, the reflex pathways were somewhat modulated at the level of the CNS. The cough response is more sensitive to increasing depth of anesthesia than any of the other respiratory reflexes such as an apneic response and decrease in the rate of breathing.[23] Differences among species also may account for these varied defense responses.[24] In clinical situations, apnea or breath-holding, rather than coughing or sneezing, is observed during mask induction of dogs and cats.[2,3,6,7]

Mask induction with these anesthetics sometimes induces an increase in HR and a decrease in MAP.[4,25] That observation suggests that the cardiovascular changes in animals during mask induction may not be a result of a nasal reflex pathway but are likely attributable to other mechanisms. In fact, it is known that stimulation of the sympathetic nervous system and the resulting arterial baroreceptor reflex, rather than airway irritation, are primarily responsible for the increase in HR and the decrease in MAP attributable to acute inhalation of 1 to 4% Iso in rabbits.[26]

It is noteworthy that the degree of respiratory reflex in response to nasal administration of these 3 halogenated volatile anesthetics was consistent with the severity of airway irritation and complications during mask induction. In humans, Hal and Iso exert greater effects than Sevo because of airway irritability, and anesthetic induction with these inhalants is sometimes accompanied by more complications such as laryngeal reflexes and struggling against inhalation.[8-11] In dogs, somatic excitement evident immediately after the onset of mask induction is observed more frequently when anesthesia is induced with Hal or Iso than with Sevo.[4]

It is widely accepted that the MAC is the standard for comparison of inhalant potencies.[11,20] In clinical situations, on the other hand, concentrations of 3 to 5% are conventionally used for Hal and Iso to allow use of mask induction to overcome the delayed increase in alveolar (end-tidal) anesthetic concentration attributable to higher blood-gas partition coefficients.[2-10] To meet pharmacologic and clinical requirements, the study reported here was designed to compare respiratory reflexes during administration of inhalation anesthetics with both MAC multiples (1.2 and 2.4 MAC) and the same vaporizer settings (5%). Although the

isolated nasal passage model used in this study did not allow us to simulate an increase in the anesthetic concentration inhaled during spontaneous respiration of each dog, it is clear that the nasal passages are the more vulnerable region when directly exposed to high concentrations (2.4 MAC or 5%) of Iso or Hal, compared with exposure to Sevo. Thus, it is better to avoid the 5% setting during mask induction with Hal, because it represents such a high MAC multiple and may depress ventilation to a much greater extent, which delays uptake. The degree of depression at 2.4 MAC of Hal was much less and not different from the degree of respiratory depression seen at 2.4 MAC of Iso. By contrast, the milder degree of nasal reflexes with Sevo may contribute to smooth and rapid onset of anesthetic effects in dogs undergoing mask induction, even when it is inspired at higher concentrations (7%, approx 3.4 MAC).[4]

It is presumed that respiratory reflexes in response to administration of inhalation anesthetics into the nasal passages are mediated by stimulation of afferent sensory neurons in the nasal mucosa. This assumption is based on the observation that the effects are considerably reduced by local anesthesia in the nasal passages.[12,17] The elicitation threshold of the laryngeal reflexes in response to chemical and mechanical stimuli is increased when nebulized lidocaine is administered locally into the airway mucosa without affecting the central neural reflex pathway.[27,28] Although we did not investigate further the origin of the reflex responses, it is known that sensory innervation of the nasal mucosa and nostrils is supplied by the maxillary (caudal nasal nerve and infraorbital nerve) and ophthalmic (ethmoidal nerve) branches of the trigeminal nerve.[14] Among these trigeminal nerve branches, which convey numerous stimuli arising from the nasal passages, the caudal nasal nerve is most vulnerable to irritants (eg, capsaicin, L-menthol and cold airflow, and distilled water) applied to the nasal mucosa of dogs.[29] In another study by our group,[17] bilateral surgical denervation of the caudal nasal nerves considerably reduced the apneic reflexes induced by nasal administration of 5% Hal, suggesting involvement of the afferent neurons of the caudal nasal nerve in eliciting the respiratory reflexes during administration of inhalation anesthetics into the nasal passages.

It remains unclear which mechanisms determine the particular sensory afferent neurons that are activated in the nasal passages during nasal administration of these inhalants. Capsaicin-sensitive unmyelinated C-fibers located in the nasal mucosa may be involved. Stimulation of airway C-fibers induces various airway defense reflexes such as apnea, coughing, sneezing, bronchoconstriction, mucus hypersecretion, and extravasation via local axons or a central pathway.[14] On the basis of in vivo single-unit recordings of the afferent neurons of the cranial (superior) laryngeal nerve, the capsaicin-sensitive receptors are uniformly stimulated by Hal, Iso, and Sevo in a dose-dependent manner, whereas other sensory receptors[30] such as respiration-modulated receptors or rapidly adapting irritant receptors had a variable response or did not respond.[30-32] It is notable that the relative responsiveness of the capsaicin-sensitive receptor to Hal, Iso, and Sevo (eg, a robust peak response followed by long-lasting activity, whereby the effects elicited by Hal and Iso were greater than those elicited by Sevo[30]) clearly corresponded to the elicitation of reflex responses to each anesthetic observed in the study reported here. The existence of capsaicin-sensitive receptors and the associated reflexive-evoked apnea in response to nasal administration of inhalation anesthetics have been documented in the nasal passages of dogs,[33,a] supporting our current hypothesis.

[a]Mutoh T. *Studies on the actions of volatile anesthetics to the sensory system in the respiratory tract of the dog.* PhD thesis, Graduate School of Agricultural and Life Sciences, University of Tokyo, Tokyo, Japan, 1998.
[b]Portex, Nihon Medical Co, Tokyo, Japan.
[c]Model KA-3020, Kimura Medical Co, Tokyo, Japan.
[d]DD102A, Toyoda Machine Works, Tokyo, Japan.
[e]Mac Lab Scope, BRC Inc, Tokyo, Japan.
[f]DX-300, Nihon Kohden, Tokyo, Japan.
[g]RT3100N, NEC-sanei, Tokyo, Japan.
[h]PC 204A, Sony Co, Tokyo, Japan.
[i]Respina 1H26, NEC-sanei, Tokyo, Japan.
[j]IL-1303, Instrumentation Laboratory Inc, Lexington, Mass.
[k]S-3, Kimura Medical Co, Tokyo, Japan.
[l]Forawic, Muraco Medical Co, Tokyo, Japan.
[m]Fluotec Mark 3, Cyprane North America Inc, Orchard Park, NY.
[n]AGM-103 Capnomac, Datex, Helsinki, Finland.
[o]Xylocaine, Astra-Japan, Osaka, Japan.
[p]NE-U12, Omron Co, Tokyo, Japan.

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