Dose-dependent Effects of Halothane on the Phrenic Nerve Responses to Acute Hypoxia in Vagotomized Dogs

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Background: Previous studies in dogs and humans suggest that the carotid body chemoreceptor response to hypoxia is selectively impaired by halothane. The present studies in an open-loop canine preparation were performed to better delineate the effects of anesthetic concentrations of halothane on the carotid body chemoreceptor-mediated phrenic nerve response to an acute hypoxic stimulus.

Methods: Three protocols were performed to study the effects of halothane anesthesia on the phrenic nerve response to 1 min of isocapnic hypoxia (partial pressure of oxygen [Pao2] at peak hypoxia, 35–38 mmHg) in unpremedicated, anesthetized, paralyzed, vagotomized dogs during constant mechanical ventilation. In protocol 1, the dose-dependent effects of halothane from 0.5–2.0 minimum alveolar concentration (MAC) on the hypoxic response during moderate hypercapnia (partial pressure of carbon dioxide [Paco2], 60–65 mmHg) were studied in 10 animals. In protocol 2, the hypoxic responses at 1 MAC halothane near normocapnia (Paco2, 40–45 mmHg) and during moderate hypercapnia were compared in an additional four animals. In protocol 3, the hypoxic response of 4 of 10 dogs from protocol 1 was also studied under sodium thiopental (STP) anesthesia after they completed protocol 1.

Results: Protocol 1: Peak phrenic nerve activity (PPA) increased significantly during the hypoxic runs compared with the isocapnic hypoxic controls at all halothane doses. The phrenic nerve response to the hypoxic stimulus was present even at the 2 MAC dose. Protocol 2: The net hypoxic responses for the two carbon dioxide background levels at 1 MAC were not significantly different. Protocol 3: The net hypoxic response of PPA for the STP anesthetic was not significantly different from the 1 MAC halothane dose. Bilateral carotid sinus denervation abolished the PPA response to hypoxia.

Conclusions: The phrenic nerve response to an acute, moderately severe isocapnic hypoxic stimulus is dose-dependently depressed but not abolished by surgical doses of halothane. This analysis does not suggest a selective depression of the carotid body chemoreceptor response by halothane. The observed hypoxic phrenic response was mediated by the carotid body chemoreceptors in vagotomized dogs because bilateral carotid sinus denervation abolished all increases in PPA. (Key words: Anesthetics, volatile: halothane. Nerves: phrenic; vagus. Receptors: carotid body chemoreceptors. Ventilation: isocapnic hypoxic ventilatory response; hypercapnia; normocapnia.)

WEISKOPF et al. first reported that halothane anesthesia impaired the ventilatory response to isocapnic hypoxia in spontaneously breathing dogs to a greater degree than the response to carbon dioxide. Subsequent studies in the same species also suggested that the hypercapnia-induced augmentation of hypoxic ventilatory drive was abolished by 1 MAC halothane. In awake humans, the hypoxic ventilatory response (HVR) to a moderate hypoxic stimulus (partial pressure of oxygen [Pao2], 44–45 mmHg) that doubled minute ventilation was reduced to less than one third at 0.1 MAC halothane and entirely eliminated at 1.1 MAC halothane. Knill and Clement presented evidence suggesting that halothane selectively depressed the peripheral chemoreflex pathway in humans. The effect of halothane on the carotid body chemoreceptor (CBCR) responses to hypoxia in cats and rabbits indicated that the CBCR response to more severe hypoxia (Pao2 < 40 mmHg) was only mildly depressed by 1% halothane. Hypoxic and hypercapnic ventilatory responses in spontaneously breathing goats were equally rather than differentially depressed, and the HVR at 0.5% halothane (= 0.5 MAC) was not significantly depressed compared with the unanesthetized
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state. Further, studies in volunteers by Temp et al challenged the human data by suggesting that 0.1 MAC of a potent inhalational agent has no effect on the HVR, although this result might be due to methodologic differences that seem to have been resolved in Knill et al. favor.

Whole-system studies in spontaneously breathing subjects are useful in describing the overall effects of inhalational agents on ventilation but do not easily allow for a clear distinction of the dominant sites and prevailing mechanisms by which an agent causes its effects. Therefore we chose an open-loop canine model that allowed us to directly study the dose-dependent effects of halothane on the central respiratory system response, in terms of phrenic nerve activity, to an acute, short, hypoxic stimulus that was solely mediated by the CBCRs. Confounding feedback loops were eliminated by vagotomy, paralysis, pneumothorax, and isocapnic mechanical ventilation of the animals independent of central respiratory output. The hypoxic stimulus was acute, severe enough to elicit a potent CBCR response, and short lived (1 min) enough to minimize effects from direct hypoxic depression of the central respiratory system.

Materials and Methods

Surgical Preparation
This research was approved by the Medical College of Wisconsin Animal Care Committee and conformed to the standards set forth in the National Institutes of Health Guide for Care and Use of Laboratory Animals. Fourteen adult mongrel dogs (weighing 8–16 kg) were studied under halothane anesthesia. These animals were used exclusively for these hypoxia studies. Airway carbon dioxide, oxygen, and halothane concentrations were continuously recorded with an infrared analyzer (POET II; Criticare Systems, Waukesha, WI) calibrated before each experiment. After induction of anesthesia via mask and tracheal intubation with auffed endotracheal tube, the lungs were mechanically ventilated with an oxygen-air mixture, and end-tidal halothane concentrations of 1.3–1.8 MAC were used for surgery. The femoral vessels were cannulated for blood sampling, blood pressure recording, and administration of maintenance fluids (isotonic saline with 0.1 mM sodium bicarbonate at 6–8 ml·kg⁻¹·h⁻¹). Phenylephrine (0.5–1.0 μg·kg⁻¹·min⁻¹) was infused when necessary to maintain mean arterial pressure at more than 75 mmHg. This was necessary for seven animals at the 2 MAC level. Esophageal temperature was maintained at 38 ± 0.5°C with a servo-controlled heating pad. The dogs were positioned prone in a stereotactic apparatus (model 1530; David Kopf Instruments, Tujunga, CA). Bilateral, dorsolateral neck dissections were performed. The right central C5 phrenic nerve rootlet was cut distally, desheathed, immersed in a mineral oil pool, and placed on bipolar platinum electrodes. The animal was paralyzed with a 0.1 mg/kg bolus and continuous infusion of pancuronium (0.15 mg·kg⁻¹·h⁻¹). Inputs from pulmonary stretch receptors and aortic arch chemoreceptors were removed by bilateral vagotomy. A bilateral pneumothorax was performed to eliminate phasic inputs from chest wall mechanoreceptors.

Carotid Sinus Nerve Denervation
After completion of protocol 1 in 6 of 10 animals, the carotid sinus region was exposed, the carotid sinus nerves were cut, and the carotid bodies destroyed by crushing and cauterizing the tissue in the sinus region. After this procedure, the anesthetic depth was decreased to 1 MAC and the hypoxic response restudied.

Recording Techniques and Data Acquisition
Effent phrenic nerve activity was amplified with a bandpass of 0.1–3 kHz, rectified, and low-pass filtered with a time constant of 100 ms to obtain a moving time average of the activity (phrenic neurogram (PNG)). The following variables were recorded continuously on a Grass (Quincy, MA) model 7 polygraph: PNG, arterial blood pressure, tracheal pressure, and airway carbon dioxide, oxygen, and halothane concentrations. Representative samples of all variables were also recorded on a digital tape system (model 3000A; A. R. Vetter, Rebersburg, PA) for later computer-assisted analysis.

Experimental Protocols
Three sets of protocols were performed to investigate (1) the dose-dependent effects of halothane anesthesia, (2) the effects of the background level of the partial pressure of carbon dioxide (Paco₂), and (3) the effects of the type anesthetic agent on the hypoxic phrenic nerve response mediated by the CBCRs.

Protocol 1: Dose-Dependent Effects of Halothane on the Hypercapnic Hypoxic Responses (10 Animals). After completion of surgery, the end tidal halothane concentration was adjusted to 0.9% (1 MAC) and maintained for at least 1 h before recordings. An open-circuit, low dead-space, solenoid valve system

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was used to ventilate the animals with an oxygen and air mixture (inspiratory pressure of oxygen [FIO$_2$], 0.30–0.45 mmHg) at a fixed rate to obtain steady-state hypercapnia (target Pa$_{CO_2}$, 60–65 mmHg) at moderate hyperoxia (target partial pressure of oxygen [Pa$_O_2$], 140–180 mmHg). This level of hypercapnia was chosen so that the animals maintained phasic phrenic nerve activity at the 2 MAC level. Moderate hyperoxia was chosen to minimize CBCR stimulation during the control state while allowing for a rapid transition to hypoxia during nitrogen breathing. End-tidal halothane, carbon dioxide, and oxygen concentrations were kept constant for at least 15 min before recording the hypoxic responses produced by subjecting the animal to 1 min of 100% nitrogen ventilation at the same tidal volume and rate as during hyperoxia via a second, computer-controlled, solenoid valve system. Arterial blood gas samples were obtained during each control period and after the last nitrogen breath (indicated by an audible signal). Before the performance of the actual protocol, a hypoxic trial run was performed to determine the appropriate hyperoxic baseline FiO$_2$ level necessary to reach the target peak hypoxic level within 1 min of 100% nitrogen ventilation.

To compensate for any time-dependent changes in phrenic nerve activity, the protocol required a return to the baseline 1 MAC halothane dose after each change in anesthetic depth. Halothane doses were thus applied in the following sequence: 1, 0.5, 1, 1.5, 2, and 1 MAC, with the last 2 MAC serving as end control (1 EC). Minimum washout times of 30 min were used whenever anesthetic depth was decreased. For the 0.5 MAC level, 0.5% halothane (equal to 0.57 MAC) was chosen because lower levels of halothane tended to cause irregular phrenic nerve activity patterns suggestive of arousal in some animals. To ensure that the animals remained anesthetized, close attention was paid to autonomic signs (salivation) and hemodynamic changes at this light level of anesthesia. All surgical interventions were performed under deep halothane anesthesia, and the 0.57 MAC runs occurred more than 1 h after completion of surgery. When observed, any phrenic changes were not consistently associated with hemodynamic changes.

Protocol 2: Effects of Background Carbon Dioxide Level on the Hypoxic Response (Four Animals). The magnitudes of the hypoxic response during normocapnia were compared with that during hypercapnia at 1 MAC halothane anesthesia in an additional four dogs. Experimental conditions were similar to those of protocol 1 except that ventilation was adjusted to produce two Pa$_{CO_2}$ levels: normocapnia (Pa$_{CO_2}$ target range, 40–45 mmHg) and hypercapnia (Pa$_{CO_2}$ target range, 60–65 mmHg). Then acute hypoxic runs with the respective Pa$_{CO_2}$ level held constant (isocapnic) were performed with the goal of reaching similar peak hypoxic levels within 1 min. Because of the larger tidal volumes during normocapnia than hypercapnia, one less nitrogen breath was required to reach the same peak hypoxic target level.

Protocol 3: Effects of Anesthetic Type on the Hypoxic Response. After completion of protocol 1, we replaced halothane in 4 of the 10 dogs with sodium thiopental (STP) to compare the relative magnitude of the hypoxic responses for these two different anesthetics. For this purpose, a 10 mg/kg intravenous bolus of STP was given after completion of protocol 1 and followed by a 4–8 mg kg$^{-1}$ h$^{-1}$ continuous infusion of STP, and then halothane was discontinued. The hypoxic responses were repeated after about 90 min when end-tidal halothane concentrations were less than 0.1%. Carotid sinus nerves were removed from the other six animals after completion of protocol 1.

All 14 animals were killed with 4% halothane and a subsequent potassium chloride bolus after data collection.

Data Analysis
Values of peak phrenic nerve activity (PPA; expressed in arbitrary units), inspiratory duration (T$_I$), expiratory duration (T$_E$), and two additional indices of inspiratory drive PPA/T$_I$, and the average slope of the PNG at 0.1 s after the onset of phrenic discharge (SLP, = [PNG(0.2) – PNG(0.2)]/0.2 s) were analyzed off-line by computer for each halothane dose at the two stimulus conditions (hyperoxic control vs. isocapnic hypoxia). Data for all respiratory parameters were averaged over 5–10 phrenic bursts during the hypoxic control states and over the two or three phrenic bursts at the maximum of the phrenic nerve response close to peak hypoxia. The averaged data for PPA and the other respiratory data were normalized to their respective values for the preceding 1 MAC halothane hyperoxic, hypercapnic control run, which was assigned a value of 1.00. The normalized data were analyzed by applying a two-way analysis of variance technique (SuperANOVA; Abacus Concepts, Berkeley, CA) with repeated measures in which the factors were anesthetic dose and Pa$_{CO_2}$ level for protocol 1; Pa$_{O_2}$ level and background Pa$_{CO_2}$ for protocol 2; and type of anesthetic agent and Pa$_{O_2}$ level for protocol 3. F-tests were used to
determine significant effects of the main factors, and modified t tests or the least significant difference method were used in testing for significant differences for planned comparisons.\textsuperscript{17,18} The planned comparisons were to test whether the hypoxic responses were significant at each anesthetic dose and whether the increasing anesthetic dose caused a significant dose-dependent depression of the hyperoxic control and the hypoxic response compared with the 1 MAC halothane dose for protocol 1. Planned comparisons for protocol 2 were made for the effect of background \( P_{a CO_2} \) on the net hypoxic response. Planned comparison for protocol 3 were made for the effect of the type of anesthetic on the hypoxic response. Data are presented as mean values with SEs unless otherwise stated. Probability levels of \( P < 0.05 \) were used to indicate significance.

Results

Protocol 1: Dose-dependent Effects of Halothane on the Hypercapnic Hypoxic Responses

Figure 1 shows a typical example of the effect of increasing halothane dose on the PNG during the hyperoxic, hypercapnic control states (first minute) followed by the acute hypoxic stimulation period (second minute into run) with the \( P_{a CO_2} \) maintained constant (isocapnic hypercapnic hypoxia). During the control period, PPA declined markedly as anesthetic dose increased from 0.5 to 2 MAC halothane. During the 1-min ventilation with 100% nitrogen (fig. 1, bottom), PPA increased and reached maximal levels close to or shortly after the last nitrogen breath. Hypoxia increased PPA at all four halothane doses. The final 1 MAC end control run (1 EC) shows good recovery of baseline phrenic activity and preservation of the hypoxic response for the duration of the protocol.

Figure 2A shows a plot of mean (±SE) normalized PPA as a function of halothane concentration for all 10 dogs. At all halothane doses, the PPA during hypoxia (hatched bars) was significantly greater than PPA of the control period (solid bars). Halothane produced a significant dose-dependent reduction in both the control PPA (fig. 2A) and the net hypoxic PPA response (fig. 2B). Very similar results were observed for the other indices of inspiratory drive such as PPA/Ti and the initial slope (SIPa Ti) of the PNG (data not shown). Four animals were neutrally apneic (phrenic nerve activity ceased) during the hyperoxic control level at 2 MAC halothane, but phrenic activity was elicited during the hypoxic stimulus. For the six dogs that were not neurally apneic at the 2 MAC control, the PPA values were 23.9 ± 4.7% and 47.6 ± 3.9% (two 14.4 ± 4.8% and 52.4 ± 4.1% for all 10 dogs) for the hypoxic control and hypoxic periods, respectively. Thus inclusion of the PPA data from the four neurally apneic dogs slightly overestimates the net hypoxic response at the 2 MAC halothane dose for the other six dogs (fig. 2B).

The final 1 MAC end-control values (fig. 2A; 1 EC) were deliberately normalized to the very first 1 MAC hyperoxic, hypercapnic control level (rather than to the 1 MAC level preceding the 2 MAC dose) to show the relative stability of the phrenic nerve preparation over the entire duration of protocol 1. The mean 1 MAC end-control value during the hyperoxic control period was 73.7 ± 18% and suggests that a moderate reduction in PPA over time had occurred. It is of note that the relative phrenic nerve response to isocapnic hypoxia...
was well preserved after return to the 1 MAC halothane levels and approximately doubled PPA each time (1.94, 2.0, 1.93, and 1.95 times control).

Plots of PPA versus PaO2 for the pooled data indicate that increasing halothane dose not only produced a downward shift in the phrenic response data but also a reduction in the average slope or sensitivity as indicated by the connecting lines (fig 2C). There were no significant differences among the PaO2 values for the hyperoxic controls, as well as, among the PaO2 values for peak hypoxia, suggesting that comparable PaO2 values existed for all halothane doses. The PaO2 levels were also consistent for all conditions, except for a small but statistically significant reduction during hypoxia at the 1.0 MAC level.

To determine whether halothane preferentially depressed the hypoxic response relative to the baseline phrenic nerve activity of the control periods, the relative sensitivities of control PPA, PPA during peak hypoxia, and the net hypoxic response to a 1 MAC increase (from 0.5 to 1.5 MAC) of halothane were compared. For this purpose the relative sensitivity was calculated as $	ext{S}_{\text{rel}} = 100 \times \frac{[1-\text{PPA(1.5 MAC)/PPA(0.5 MAC)}] / 1 \text{ MAC}}{}$, and indicates the amount of reduction (%) in these variables produced by a 1 MAC increase in halothane concentration. The mean sensitivities were $	ext{S}_{\text{rel}}$ hyper-
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RESPIRATORY PHASE DURATIONS

END-TIDAL HALOTHANE CONC. (MAC)

Fig. 3. Effects of halothane concentration and hypoxia on inspiratory duration, $T_i$, (upper panel) and expiratory duration, $T_e$, (lower panel). $T_i$ decreased during the hyperoxic hypercapnic control for the 1.5 and 2 MAC dose ($P < 0.05$; $***P < 0.001$). Hypoxia increased $T_i$ only at the 2 MAC dose compared with the hyperoxic control ($**P < 0.001$). $T_e$ increased at the 2 MAC dose during the hyperoxic control ($**P < 0.001$). Hypoxia shortening $T_e$ at the 0.5 and 2 MAC dose ($P < 0.05$; $*P < 0.01$).

oxic control PPA) = 59.7 ± 4%, $S_{oxi}(hypoxia$ PPA) = 65.1 ± 3%, and $S_{net}(net PPA) = 64.4 ± 5.1%$. A repeated one-way analysis of variance and paired comparisons indicated no significant differences among these variables.

Effect of Halothane Dose and $P_{aO_2}$ Level on Respiratory Timing. During the hyperoxic control period, an increase in the halothane dose caused a statistically significant shortening of $T_i$ at the 1.5 and 2 MAC doses compared with the 1 MAC control dose (fig. 3, upper). Hypoxia increased $T_i$ only at the 2 MAC dose. The effect of halothane on the hyperoxic control period $T_e$ was only evident at 2 MAC (fig. 3, lower). There was a tendency for hypoxia to produce a shortening of $T_e$. This effect reached significance for the 0.5 and 2 MAC doses. The average $T_i$ and $T_e$ at the first 1 MAC halothane level were 1.73 ± 0.19 s and 3.24 ± 2.28 s for the hyperoxic control condition. For the four dogs that became neurally apneic at 2 MAC, dummy values based on the mean values for $T_i$ and $T_e$ obtained for the other six dogs were used. Adding these dummy values or eliminating the 2 MAC data for the four neurally apneic dogs did not substantially alter the overall results.

Effect of Carotid Sinus Nerve Denervation. Figure 4 shows a representative example of the effect of bilateral carotid body denervation at the 1 MAC halothane dose. The increase in PPA that is seen during the hypoxic stimulus in the intact animal (top trace) is completely abolished by bilateral carotid sinus denervation (CSN cut, middle trace). The pooled data from six denervated animals indicated that none of the indices of inspiratory drive changed significantly with the hypoxic

Fig. 4. Phrenic nerve responses (PNG) to acute isocapnic hypoxia before (top) and after carotid body chemoreceptor denervation during 1 MAC halothane anesthesia. $O_2$ (%), airway oxygen concentration. The increase in phrenic nerve activity during hypoxia (60–120 s) is abolished, indicating that the observed response is mediated by the carotid body chemoreceptors. Also note the absence of any centrally mediated depressant effects of hypoxia in the denervated animal.

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stimulus at the 1 MAC dose (values of control vs. hypoxia for PPA: 100% vs. 105.9% ± 4.1; SLP(0.1): 100 vs. 102.7 ± 6; PPA/Ti: 100 vs. 101.3 ± 8.3).

Protocol 2: Comparison of Hypoxic Responses at Different Background Carbon Dioxide Levels: Normocapnia Versus Hypercapnia

In four additional dogs, hypoxic responses during normocapnia were compared with those during hypercapnia. An example from one of these dogs shows that the increase in background PaCO₂ from near normocapnia (43.1 mmHg) to moderate hypercapnia (65.9 mmHg) produced about a 100% increase in PPA during the control hypoxia period (left part of fig. 5A). The net isocapnic hypoxic response during hypercapnia was about 100% of control PPA, which is similar to the response magnitude obtained in the 10 dogs of protocol 1 (94.4 ± 8.7%), but the net isocapnic hypoxic response during normocapnia was about 35% more than during hypercapnia in this particular animal. However, analysis of the pooled data for all four dogs indicated no significant differences in the net hypoxic responses for the two carbon dioxide levels as shown in figure 5B. The average net hypoxic response during normocapnia was 90.7 ± 22.4% and during hypercapnia was 82.1 ± 14.9%. During normocapnia, the mean (±SE) PaO₂ values were 158.6 ± 11.1 mmHg and 34.0 ± 1.08 mmHg for hyperoxia and hypoxia, respectively, and during hypercapnia they were 134.7 ± 14.4 mmHg and 35.9 ± 1.2 mmHg, respectively. There was no difference between the peak hypoxic PaO₂ values for the normocapnic and hypercapnic conditions.

Protocol 3: Effect of Anesthetic Agent on Hypoxic Responses: Halothane Versus Thiopental

After completion of protocol 1 in 4 of the 10 dogs, halothane was discontinued and replaced by STP anesthesia. Hypoxic responses were then obtained 90 min after halothane. An example of the responses from one of the animals for the 1 MAC dose preceeding and during STP anesthesia indicates that the net hypoxic responses for PPA are comparable (fig. 6A). Analysis of the pooled data from four animals also indicates no significant differences in the net responses for PPA (fig. 6B). The peak hypoxic stimuli for the 1 MAC halothane run (directly preceding STP) and for the STP anesthesia are comparable but slightly more potent than those for protocol 1 (fig. 2C), and they explain why the net hypoxic PPA response at 1 MAC halothane for these four animals slightly exceeds the group mean of protocol 1. It is readily apparent that Ti and TE values significantly differ between these two anesthetic agents.

Discussion

The principle finding of the present studies is the persistence of the CBCR-mediated central inspiratory response to a moderately severe, acute hypoxic stimulus during hypercapnia (PaCO₂, 60–65 mmHg) under halothane anesthesia (0.5–2 MAC). At 2 MAC the net hypoxic response, in terms of PPA, was depressed to 40.4% of the 1 MAC net hypoxic response. At 1 MAC, the acute hypoxic stimulus of PaO₂ = 38.3 ± 1.4 mmHg produced a net increase in PPA of 94.4 ± 8.7% during moderate hypercapnia. A net increase of similar magnitude was observed during normocapnia (fig. 5B). This suggests that the effects of halothane on the hypoxic responses obtained during hypercapnia were not exaggerated secondary to a hypoxic–hypercapnic interaction and may be taken as representative of those expected during normocapnia. Hypercapnia was used to prevent apnea at 2 MAC halothane, but 4 of 10 animals became apneic at this level during the hypoxic control period.

Open Loop Conditions

The main purpose of this study was to evaluate the depressant effects of halothane on the hypoxic CBCR-mediated response of the central respiratory motor pathways. The effects of the anesthetic, hypoxia, or both distal to the phrenic motoneurons were eliminated in this investigation. Surgical doses of halothane can have depressant effects at the neuromuscular junction, the diaphragm, and on lung and chest wall mechanics. Other inputs and secondary effects were either eliminated or controlled. Cervical vagotomy was used to eliminate inputs from the aortic arch chemoreceptors, which mainly mediate phase-timing effects without affecting inspiratory drive (i.e., PPA), and to eliminate pulmonary stretch receptor inputs that alter Ti, TE, and PPA. A bilateral pneumothorax in conjunction with paralysis minimized or eliminated phasic proprioceptive inputs from chest wall mechanoreceptors and influences due to changes in the mechanical properties of the lung and chest wall. Mechanical ventilation ensured a constant level of isocapnic hypercapnia during both the hypoxic control states and the hypoxic runs, regardless of central inspiratory output.
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Fig. 5. (A) Effect of two levels of background $P_{a\text{CO}_2}$ on phrenic nerve activity (PNG) during the hyperoxic control period and during isocapnic hypoxia at 1 MAC halothane (protocol 2). $O_2$ (%), airway oxygen concentration. (B) Plot of peak phrenic activity (PPA) versus $P_{a\text{CO}_2}$ (n = 4; protocol 2). There were no significant differences in the net PPA hypoxic responses for the two $P_{a\text{CO}_2}$ levels.

Peripheral and Central Effects of the Hypoxic Stimulus

To minimize any central depressant effects of hypoxia, we deliberately chose an intense but short hypoxic stimulus that would produce a strong stimulation of the CBCRs before the onset of central hypoxic depression. The onset of the central depressant effect is delayed by 30 s and develops slowly (time constant, $\approx 150$ s$^{24}$), but there is evidence in humans that halothane anesthesia might decrease some central time constants,$^{11}$ and thus the depressant effects of hypoxia might become apparent even faster. The carotid sinus denervation performed in a subset of the animals confirmed that our short hypoxic stimulus did not cause central hypoxic depression of phrenic nerve activity (see fig. 4 for example). In addition, the transient nature
Fig. 6. (A) Effect of isocapnic hypoxia on phrenic nerve activity (PNG) during 1 MAC halothane anesthesia and 90 min after replacement of halothane with intravenous STP anesthesia. The two anesthetics have strikingly different effects on neural phase timing, but the hypoxic stimulus caused a comparable increase in peak phrenic activity with both anesthetics. O₂ (%), airway oxygen concentration. (B) Pooled peak phrenic activity (PPA) data versus PaO₂ of the four animals subjected to the hypoxic stimulus with two different anesthetics (protocol 3). There were no significant differences between the net phrenic hypoxic responses for the two anesthetics. STP = sodium thiopental; HAL = halothane.

of our hypoxic stimulus would minimize a possible mild MAC requirement–lowering effect due to hypoxia.²⁵

An underestimation of the true hypoxic response, especially at the lower levels of anesthesia, may have occurred due to an increase in baroreceptor activity secondary to a transient, hypoxia-induced increase in blood pressure. Baroreceptor stimulation inhibits respiration in the dog, mainly by decreasing respiratory rate rather than tidal volume (or PPA).²⁶,²⁷ However, because the peak of this blood pressure increase was typically delayed beyond the peak phrenic response to hypoxia, its influence would have been minimal. Another possible source of underestimation of the peak hypoxic phrenic response is the short duration of our hypoxic stimulus, which might not have allowed sufficient time for the full response to develop. However, because similar peak
hypoxic levels were obtained at all halothane doses, such an underestimation should have been of similar relative magnitude at all halothane doses.

Peripheral and Central Components of Chemodrive

Halothane produced dose-dependent reductions in PPA during hyperoxia and hypoxia (fig. 2A), and also in the net response (fig. 2B). The net response represents the average sensitivity of PPA to oxygen pressure over the hyperoxic-to-hypoxic range (line slopes in fig. 2C). In contrast, the PPA during hyperoxia mainly reflects excitation due to central carbon dioxide-sensing mechanisms because during hyperoxia the contribution from the peripheral chemoreceptors to ventilation mediated by carbon dioxide is likely to be <25%. Thus the depressant effects of halothane on the central chemosensory-mediated component of PPA during hyperoxia would account for a large amount of the downward shifts in the PPA versus PaO2 plots (fig. 3A).

In terms of minute ventilation, the Leiden group, using an artificial brain stem perfusion technique in cats, showed that there is no interaction between peripheral oxygen and carbon dioxide and central carbon dioxide stimuli and that the peripheral and central components of chemodrive are simply additive. Similarly, the net PPA responses to the same hypoxic stimulus were of similar magnitude for normocapnic and hypercapnic baseline conditions (fig. 6B). Thus it appears that the dose-dependent reduction in the net PPA represents the depression of the hypoxic component of the PPA, rather than nonlinear changes in hyperoxic PPA due to halothane.

The sensitivities (Shyp) of the net PPA response, the hyperoxic PPA, and the hypoxic PPA to a 1 MAC halothane dose increase were not different from one another. This suggests that a selective depression by halothane of the CBCR-mediated contribution to PPA did not occur, but rather that the depressant effect of halothane was of a similar degree and common to peripheral and central chemosensory mechanisms and pathways. This finding corresponds to that of van Dissel et al., who showed that halothane when administered systemically, with the exception of the brain stem, against a background of chloralose-urethane anesthesia, depressed the peripheral and central responsiveness to carbon dioxide equally. They suggested that the main depressant effect of peripheral halothane on the overall ventilatory response to carbon dioxide is located in structures common to both the peripheral and central chemoreflex; that is, the neuromechanical link between brain stem centers and respiratory movements (motoneurons, respiratory muscles, or lung elastance). Our data suggest that halothane depression of common pathways, mechanisms, or both occur within the brain stem as well. The sensitivities of the phrenic activities to halothane may be due to halothane-induced changes in chemosensitivity or apneic threshold involving the sensors and associated neural pathways. This is also supported by the fact that halothane produces a dose-dependent depression of the discharge frequency of inspiratory bulbospinal neurons within the ventral respiratory group of the medulla. Furthermore, the sensitivity of PPA to halothane was significantly greater than that of the peak discharge frequency of the inspiratory neurons, suggesting an additional depressant effect of halothane on the phrenic motoneurons.

The method we chose to compare the sensitivities of peripheral and central components to halothane overcomes many of the interpretation problems associated with comparing the ratios, PPA(hypoxia) to PPA(hyperoxia), at each halothane dose. For example, assuming that the central and peripheral components are additive, if halothane depressed the central but not the peripheral component, a downward but parallel shift in the PPA versus oxygen pressure plot would be seen, but there would be significant increases in the PPA(hypoxia)-to-PPA(hyperoxia) ratio, especially because PPA(hyperoxia) became small at the higher halothane doses. Such findings might be interpreted as an increase in the responsiveness of the system to the hypoxic stimulus, when there was, in fact, no effect of halothane on the peripheral component at all (i.e., no change in response slope).

Estimated Magnitude of Halothane Depression

Although avoidance of background anesthesia allowed us to accurately assess the dose-dependent effects of halothane alone on the hypoxic response, the lack of a drug-free control state does not allow us to study the effects of halothane per se. We previously discussed the two main alternatives to our approach with halothane alone,14 decerebration or parenteral background anesthesia, but these have severe limitations of their own.14,31 To estimate the depressant effect of 1 MAC halothane on PPA relative to the awake state, we have used published tidal volume values, because PPA and tidal volume are highly correlated.32 Using tidal volume versus PaO2 relations obtained in spontaneously breathing halothane-anesthetized15 and awake dogs,34,35 the estimated reduction in tidal volume by 1 MAC halothane, under isocapnic conditions, is about 51% of awake values. The relations we found between

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PPA and increasing halothane dose are linear (fig. 2A; 
\[ r = 0.99 - 1.0 \); when extrapolated values to 0 MAC (i.e., 
awake) are used, the estimated depression at 1 MAC is 
46% for hyperoxia (44% for hypoxia), which is not very 
different from the depression estimates derived from the 
tidal volume data (51%). Because the net hypoxic 
PPA and hypoxic PPA were depressed by halothane 
to the same extent, this suggests that the net hypoxic 
PPA response at 1 MAC also would be depressed by 
about 50% compared with 0 MAC.

Using minute ventilation data, Weiskopf et al.\(^1\) reported a 
52 - 65% depression of the awake ventilatory response 
by 1.1% halothane (1.2 MAC) to a hypoxic stimulus of 
\( P_{O_2} \) of 40 mmHg (\( P_{O_2} \), 40 - 48 mmHg). The magnitude 
of our hypoxic stimulus was similar and the net PPA 
responses produced were of the same magnitude for normo-
capnia and hypercapnia (fig. 5B). In addition, the net hy-
opxic PPA response for 1 MAC halothane was not different 
from that for STP (fig. 6B), which also suggests that haloth-
ane does not selectively depress the CBCRs. Hirshman 
et al.\(^6\) reported that the isocapnic hypoxic response (mi-
nute ventilation) in dogs during thiopental anesthesia was 
62% of the awake response. Thus a 50% reduction in our 
net PPA response to hypoxia at 1 MAC compared with 
awake appears to be a reasonable estimate.

**Hypoxic-Hypercapnic Interaction**

It has been suggested that halothane impairs or even 
reverses the synergistic interaction between hypercapnia 
and hypoxia at the CBCRs in spontaneously breathing 
conscious animals.\(^1,2\) At 1 MAC halothane, the magnitude 
of the net hypoxic PPA was no different for hypercapnia 
than for normocapnia (fig. 5B). This apparent lack of syn-
ergism may be explained by the phenomenon known as 
"progressive saturation," \(^3\) which may have attenuated 
the hypercapnic-hypoxic response, because the magni-
uide of the PPA during hyperoxic-hypercapnia was 67% 
greater than during hyperoxic-normocapnia. In addition, 
because our animals were vagotomized, any effects of 
halothane on hypoxia-induced increases in respiratory rate 
after the aortic arch chemoreceptors cannot be assessed in 
our reduced preparation.

**Comparison of Human and Animal Studies**

Studies by Knill and colleagues and more recently by 
Dahan et al.\(^11\) leave little doubt that the HVR to modest 
levels of isocapnic hypoxia (\( P_{O_2} \) of \( \approx 50 \) mmHg, oxygen 
saturation of 80%) is severely blunted in humans at su-
banesthetic halothane concentrations.\(^3,10,11\) Knill’s stud-
ies also suggest that 1.1 MAC halothane, enfurane, or 
isoflurane completely abolish the response to this level 
of hypoxia in humans, although a study by Sjogren et al.\(^18\) found that the poikilocapnic HVR is maintained 
at 0.6 MAC isoflurane, whereas the isocapnic HVR is 
depressed by 50% but not abolished. The question arises 
why the human studies show such a profound, appar-
tently selective depression of the peripheral chemore-
response to hypoxia in contrast to a more moderate and 
less selective effect in our canine studies and other 
animals. Dahan et al.\(^11\) suggest that species differ-
ences are responsible. In cats, peripheral and central 
chemosensitivity are depressed by halothane to the same extent.\(^28\) Similarly, data by Koh and Severinghaus\(^7\) in 
spontaneously breathing tracheotomized goats indi-
cate that the hypoxic and carbon dioxide chemosensi-
tivities were depressed equally. At \( \approx 0.5 \) MAC end-tidal 
concentration, halothane did not significantly depress the 
hypoxic response (\( P_{O_2} \) of 40 mmHg).

In cats\(^5,6\) and rabbits,\(^6\) halothane depresses CBCR activity 
during moderate hypoxia, but essentially no depression 
was observed when \( P_{O_2} \) was \( < 40 \) mmHg. Thus it is pos- 
sible that halothane produces its effect by shifting the hy-
perbolic relation between CBCR activity and \( P_{O_2} \) toward 
lower \( P_{O_2} \) values, as suggested by Koh and Severinghaus.\(^7\) 
To determine whether the oxygen response threshold 
of the CBCRs in humans is shifted to lower \( P_{O_2} \) levels 
by halothane would require a more severe hypoxic stimulus, 
which is ethically unacceptable.

We conclude that the phrenic nerve response to a mod-
erate to severe, short isocapnic hypoxic stimulus during 
moderate background hypercapnia was dose dependently 
depressed but not eliminated by surgical doses of haloth-
ane in an open-loop canine model. The observed re-
sponses were mediated by the CBCRs, because bilateral 
carotid sinus nerve denervation abolished them. Analysis 
of the relative sensitivities of hypoxic versus hyperoxic 
peak phrenic nerve activity to a 1 MAC dose increase of 
halothane does not suggest a selective depression of the 
CBCRs versus the central chemoresponse by the anesthe-
tic. In addition, the net hypoxic responses for 1 MAC 
halothane and STP anesthesia were no different. The net 
hypoxic responses for two carbon dioxide background 
levels (normocapnia versus hypercapnia) at 1 MAC hal-
othane also were not different, suggesting a lack of syner-
gistic effects between hypoxia and hypercapnia during 
halothane anesthesia.

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