Anesthesiology
60:19–24, 1984

Comparison of Changes in the Hypoglossal and the Phrenic Nerve Activity in Response to Increasing Depth of Anesthesia in Cats

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The effects of increasing depths of anesthesia on the activities of the hypoglossal nerve (HN) and the phrenic nerve (PN) were investigated in artificially ventilated, vagotomized cats. An abrupt increase in inspired concentration of halothane from 1% to 4% immediately decreased both HN and PN activities, but HN activity decreased more and disappeared much earlier than did PN activity. Steady-state responses of HN and PN activities to changes in end-tidal concentration of halothane showed that halothane depressed both HN and PN activities in a dose-related manner but at different rates, suggesting that respiratory control of the tongue muscles and the diaphragm are in part mediated by different neural pathways. Differential suppression of PN and HN activities also was observed following an acute increase in anesthetic depth with thiopental and diazepam. In contrast, no such differential suppression was observed following ketamine administration. Thus, differential suppression of PN and HN may be associated not only with depth of anesthesia but also with the type of anesthetic used. (Key words: Anesthetics, intravenous: thiopental; ketamine. Anesthetics, volatile: halothane. Hypnotics: benzodiazepines, diazepam. Nerve: hypoglossal; phrenic.)

PHASIC INSPIRATORY ACTIVITY of upper-airway muscles plays an important role in maintaining a patent pharyngeal and laryngeal airway.[1] It is well known that ineffective or inadequate activation of upper airway muscles during anesthesia frequently leads to hypoventilation and asphyxia from obstruction of the upper airway,[2] indicating the vulnerability of upper airway function to anesthesia. Although the study of Brouillette and Thach[3] showed that deep anesthesia in rabbits depresses tongue muscle activity more than diaphragmatic activity, no systematic examination of the effect of anesthesia on the activity of the upper airway muscles has been reported. In the present study, we attempted to examine the effects of increasing depths of anesthesia on the activity of the hypoglossal nerve, which innervates the tongue muscles, and on the activity of the phrenic nerve, which innervates the diaphragm.

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Received from the Departments of Anesthesiology and Physiology, School of Medicine, Chiba University, Chiba, Japan. Accepted for publication June 28, 1983. Supported in part by Grant 58570630 for Scientific Research from the Ministry of Education, Science and Culture of Japan.

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Methods

Experiments were performed on 18 adult cats weighing 2.9 to 4.4 kg. Anesthesia was induced and maintained with 2–3% halothane in oxygen using a precalibrated halothane vaporizer (Fluotec Mark 2) during the surgical preparation of the animals. The animals were fixed in a supine position. Tracheostomy was performed, and the trachea was cannulated. The right femoral artery was cannulated for the measurement of arterial blood pressure and for blood sampling. The right femoral vein also was cannulated for infusion of drugs and saline. Bilateral vagotomy was performed at the middle cervical level. The hypoglossal nerve (HN) and a root of the phrenic nerve (PN) were exposed, desheathed, and cut. Their central ends were placed on bipolar silver electrodes in a pool of warm liquid paraffin and prepared for recordings. Both HN and PN activities were amplified by a.c. amplifiers with 100-Hz and 3000-Hz low- and high-frequency filters. The rectified signals of the amplified signals were integrated by leaky R-C integrators having a time constant of 100 ms to obtain moving average outputs. After the surgical preparation, the animals were paralyzed with pancuronium bromide (0.2 $mg \cdot kg^{-1}$) and artificially ventilated at a fixed rate and volume (rate × volume: 20 × 40 ml). Then, halothane in a concentration of 1.0% in oxygen was administered. The rectal temperature of the animals was maintained at about 38° C by a heating lamp. End-tidal P_{CO_2} ($P_{ET}CO_2$) was monitored continuously with an infrared CO_2 analyzer (Minato MEL RAS-41) and was controlled at desired levels by introducing small amounts of CO_2 into the inspired gases. PN activity, HN activity, their moving average outputs, $P_{ET}CO_2$, and arterial blood pressure all were recorded on ultraviolet-sensitive paper. The status of arterial blood gases was checked occasionally by measuring P_{CO_2}, P_{O_2}, and *p*H with a Radiometer® blood gas analyzer (BM2 MK2). If there was evidence of severe metabolic acidosis, sodium bicarbonate was administered to correct it.

EXPERIMENTAL PROCEDURES

In eleven of 18 cats, the responses of PN and HN activities to deepening halothane anesthesia were investigated in two ways: 1) transient responses, and 2) steady-state responses. The transient responses of PN and HN activities to deepening halothane anesthesia were ex-

amined by abruptly changing the inspired concentration of halothane from 1.0 to 4.0% at a constant $P_{ET}CO_2$ of 40–45 mmHg. Administration of 4.0% halothane was continued until phasic respiratory activity in both PN and HN disappeared. At this point halothane was discontinued. The steady-state responses of PN and HN activities were examined at four different depths of halothane anesthesia (0.8, 1.1, 1.4, and 1.7 MAC) at a constant $P_{ET}CO_2$ level of 55–60 mmHg. One MAC for halothane in cats was taken as 0.82% end-tidal concentration.[4] End-tidal halothane concentrations were measured with an ultraviolet halothane analyzer (Minato MEL RAS-51). PN and HN activities were measured at least 15 min after establishing a constant halothane concentration.

In another seven cats, the transient responses of PN and HN activities to bolus injections of thiopental (2.0 $mg \cdot kg^{-1}$), ketamine (1.0 $mg \cdot kg^{-1}$), and diazepam (0.2 $mg \cdot kg^{-1}$) were examined at a constant $P_{ET}CO_2$ of 40–45 mmHg, while baseline anesthesia was maintained with halothane (0.8 MAC halothane). The order of injections was randomized. Following the administration of each agent, sufficient time (usually 15–20 min for thiopental and ketamine and 45–50 min for diazepam) was allowed before the administration of the next agent to enable arterial blood pressure, PN activity, and HN activity to return to approximately the baseline level (control).

The intensity of PN and HN activities associated with each burst was quantified by the peak height of the moving average representation. For the purpose of comparing various animals, percentage changes in nerve activities were calculated using a value of 100% for the activity at 0.8 MAC halothane (control). Statistical analysis was performed using Student's *t* test where appropriate.

Results

Transient Responses of HN and PN Activities to an Acute Change in Depth of Halothane Anesthesia

Figure 1 shows changes in HN and PN activities following a sudden change in inspired concentration of halothane. Anesthesia initially was maintained with an inspired concentration of 1.0% halothane, and the animal had stable HN and PN activities (baseline level). With the start of administration of 4.0% halothane, both HN and PN activities decreased progressively to the point where no phasic respiratory activity in both nerves was observed (fig. 1*A*). During the course of respiratory depression, the decrease in HN activity was more pronounced than the decrease in PN activity, and rhythmic discharge of HN disappeared much earlier than that of PN. During the recovery period following discontinuation of halothane (fig. 1*B*), both HN and PN activities recovered gradually. However, the reinitiation of phasic activity

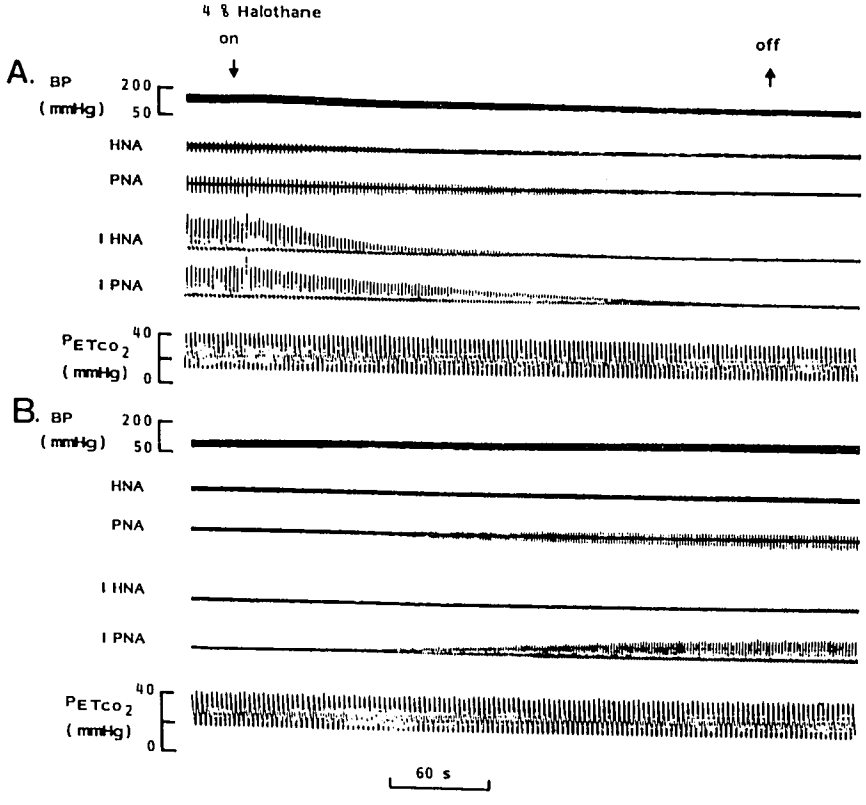

FIG. 1. Effects of a sudden change in inspired concentration of halothane on HN and PN activities. Note that HN activity disappeared before PN activity following administration of 4% halothane and PN activity resumed before HN activity following discontinuation of halothane. A and B were continuous. (BP = arterial blood pressure; HNA = hypoglossal nerve activity; PNA = phrenic nerve activity; IHNA = integrated hypoglossal nerve activity; IPNA = integrated phrenic nerve activity.)

in PN was much earlier than that of HN. It took about 15 min for both HN and PN activities to return to the baseline level. Similar changes in HN and PN activities were observed consistently in all animals. These observations indicate that HN activity is more vulnerable to the depressant effect of halothane.

Steady-state Responses of HN and PN Activities to Increasing Depth of Halothane Anesthesia

Like the transient responses, increases in anesthetic depths progressively decreased both HN and PN activities during steady-state response tests. Figure 2 shows HN and PN activities at four different depths of halothane anesthesia. It can be seen that both HN and PN activities decreased with increases in depth of halothane anesthesia but that decreases in HN activity were more prominent than decreases in PN activity. Progressive decreases in arterial pressure and heart rate also were observed as the level of anesthesia advanced. The effects of increasing depths of halothane anesthesia on HN and PN activities for all animals are summarized in figure 3. There were significant differences between HN activity and PN activity at 1.1, 1.4, and 1.7 MAC halothane ($P < 0.01$).

Changes in PN and HN Activities Following Administration of Various Intravenous Agents

Figure 4 shows changes in PN and HN activities obtained in a single cat following administration of thiopental, ketamine, and diazepam. The maximum depression of PN and HN activities occurred 30–35 s after intravenous injection of thiopental, at which time PN activity was 50% of baseline activity, while HN activity was 15% of baseline activity. Ketamine produced the maximum depression of PN and HN activity 25–45 s after intravenous injection, at which time PN activity was 55% of baseline activity, while HN activity was 40%. The maximum depression of PN and HN activity occurred 40–45 s after intravenous injection of diazepam, at which time PN activity was 50% of baseline activity, while HN activity was 35%. Effects of the three intravenous agents obtained in all the animals are shown in figure 5. There was no significant difference in activity between PN and HN following ketamine administration. In contrast, HN activity was depressed more than PN activity following thiopental and diazepam administration.

Discussion

In the present study, experiments were performed in the vagotomized state because of technical reasons. First, in order to measure the precise values of end-tidal halothane concentration with the halothane analyzer used in this study, a tidal volume of at least 40 ml was needed. Second, with this tidal volume intact, vagus nerves led to a marked variation in PN and HN activities caused by respirator-induced stimulation of lung receptors. Although the procedure of vagotomy may influence the responses of PN and HN activities to increasing depths of anesthesia, we made no systematic examination of the

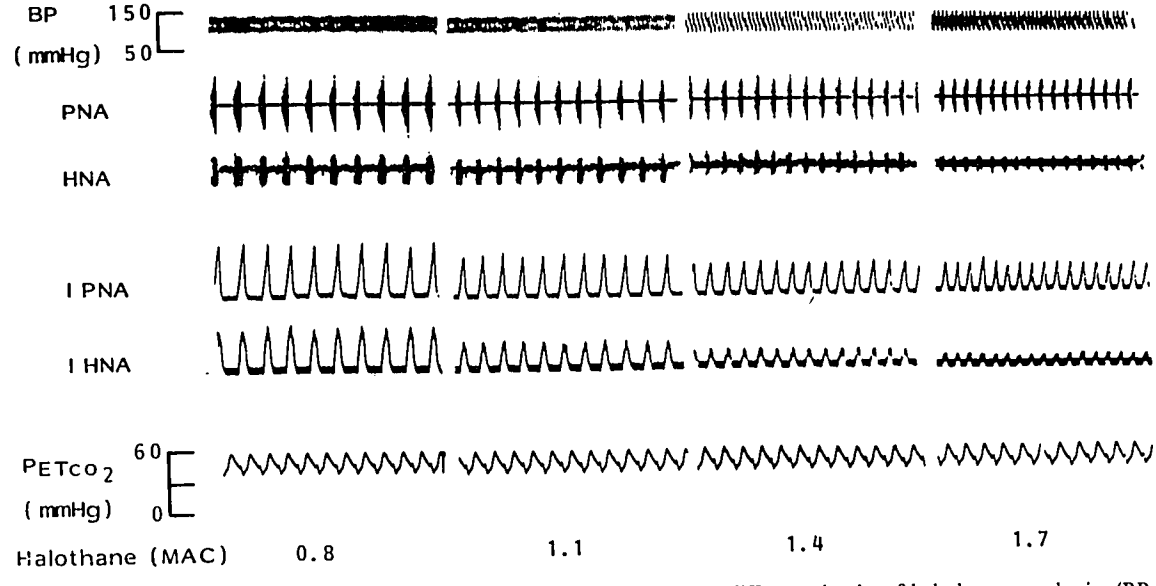

FIG. 2. Experimental records illustrating changes in PN and HN activities at four different depths of halothane anesthesia. (BP = arterial blood pressure; HNA = hypoglossal nerve activity; PNA = phrenic nerve activity; IHNA = integrated hypoglossal nerve activity; IPNA = integrated phrenic nerve activity.)

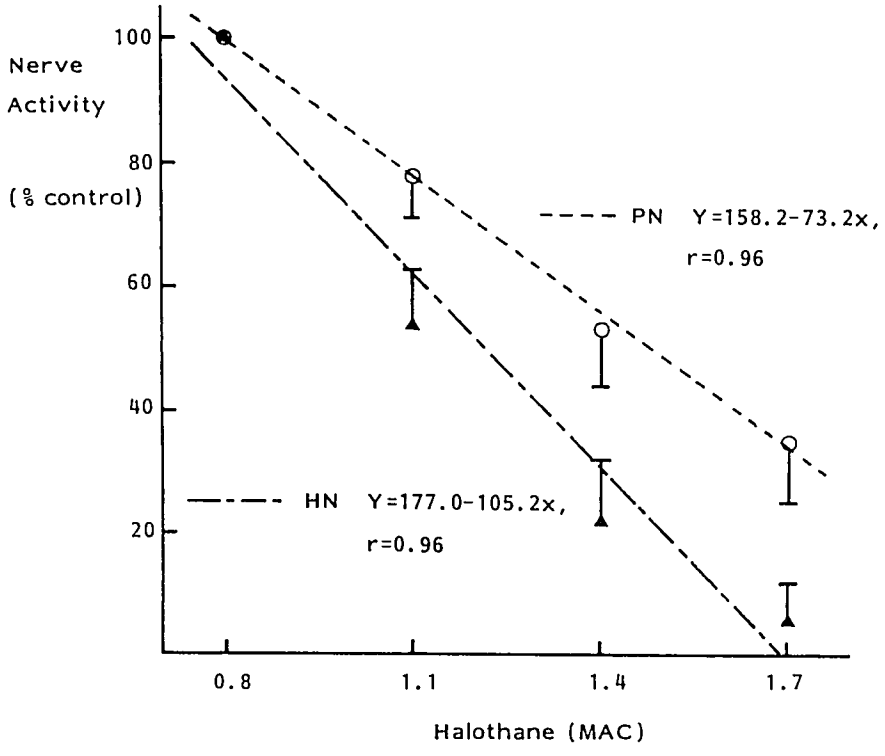

FIG. 3. Effects of increases in anesthetic depth on PN and HN activities. Open circle indicates PN activity and closed triangle represents HN activity. Values are mean ± SD. Linear regression relationships, calculated by the method of least square, also are shown.

effects of vagotomy in the present study. In humans, pulmonary stretch receptor effects on respiration are much less pronounced than in animals,[5] and thus the state in humans may resemble that in vagotomized animals.

Although it generally is accepted that respiratory activity in the cranial nerves supplying upper airway muscles is more sensitive to the depressant effect of anesthesia than PN activity,[6-8] this difference in sensitivity never has been assessed in a quantitative manner. Brouillette and Thach[3] examined the effects of anesthesia on the genioglossus and the geniohyoid muscle activity in rabbits and showed that deep anesthesia with pentobarbital or ether depressed the airway-maintaining activity of these muscles more than the diaphragm activity. However, in their study neither the level of anesthesia nor the background chemical drive of respiration was controlled in a

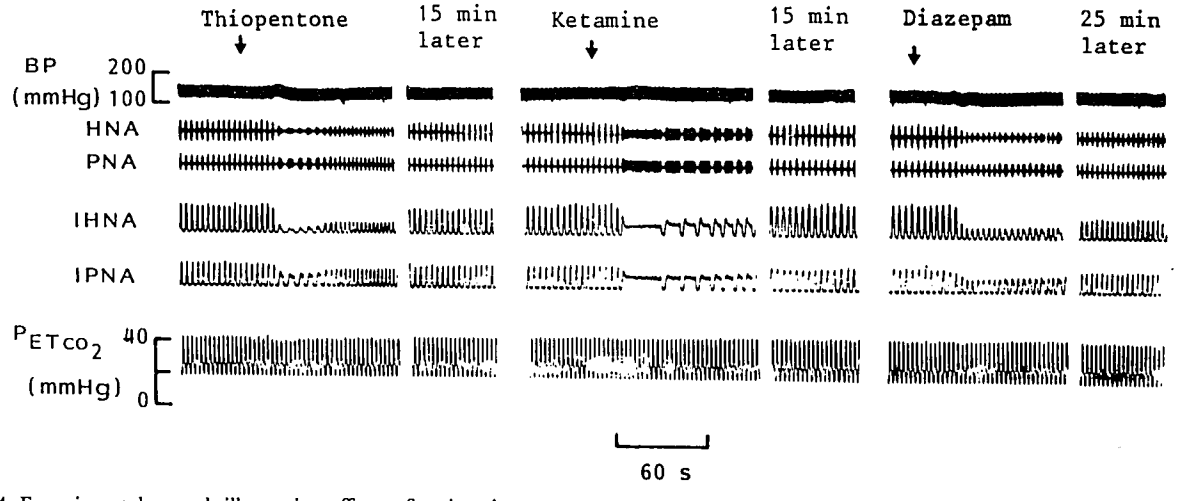

FIG. 4. Experimental records illustrating effects of various intravenous agents on PN and HN activities. (BP = Arterial blood pressure; HNA = hypoglossal nerve activity; PNA = phrenic nerve activity; IHNA = integrated hypoglossal nerve activity, IPNA = integrated phrenic nerve activity.)

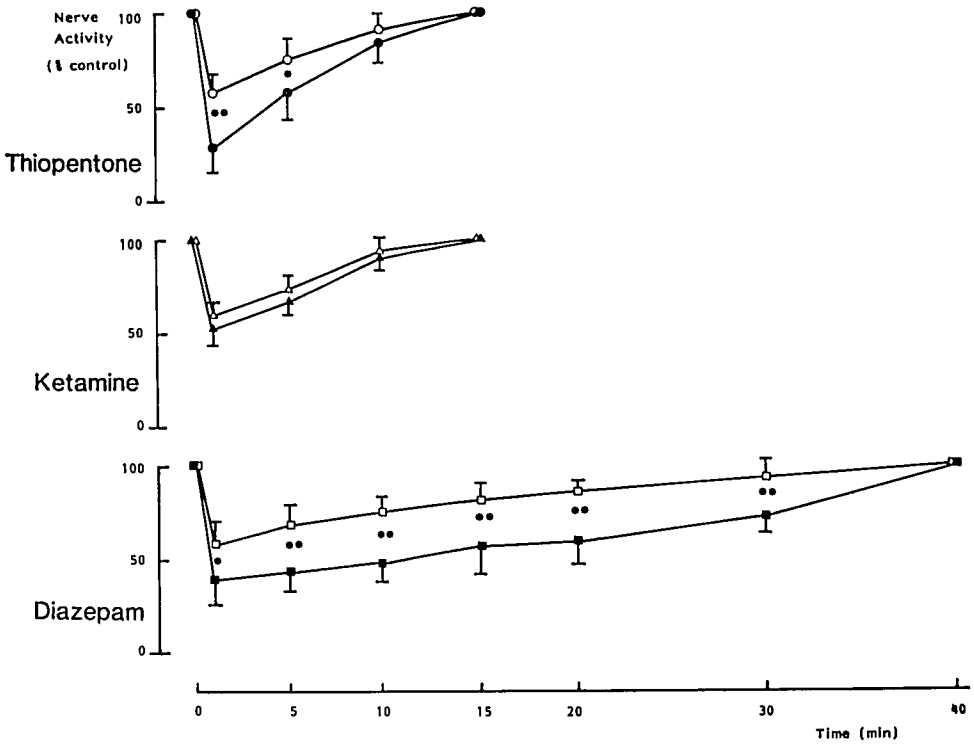

FIG. 5. Time course of recovery of PN and HN activities following intravenous injections of thiopental, ketamine, and diazepam. Values are mean ± SD. Open symbols indicate PN activity and solid symbols represent HN activity.

precise manner. In contrast, in our study the depth of halothane anesthesia was controlled precisely by measuring end-tidal halothane concentrations, and the background chemical drive was kept constant by maintaining $P_{ET}CO_2$ at a constant level. Our results showed that increasing depths of halothane anesthesia from 0.8 to 1.7 MAC progressively decreased both PN and HN activities but at different rates. This indicates that the effect of halothane on HN activity is qualitatively similar but quantitatively different from its effect on PN activity.

The observation of quantitatively different responses of these two nerves to increasing depths of halothane anesthesia is quite analogous to the observation of Weiner *et al.*[9] that there are differences in HN activity and PN activity in response to changes in chemical stimuli. Weiner *et al.*[9] showed that in dogs, hypercapnia and hypoxia, alone and in combination, similarly increased both HN and PN activities but at different rates. Also, Brouillette and Thach[10] observed that in rabbits both hypercapnia and hypoxia increased the activity of the genioglossus muscle more than that of the diaphragm. Although mechanisms and factors that cause quantitative differences in the responses of HN and PN activities to changes in chemical stimuli are unclear, similar mechanisms and factors are likely responsible for producing the differential suppression of HN and PN activities during respiratory depression due to increasing depths of halothane anesthesia.

The differences between the two nerves' activities during respiratory stimulation and depression suggest that control of the tongue muscles and the diaphragm may be mediated in part by different neural pathways. There is evidence that in the medulla, specific neuronal pools project to specific respiratory muscles and that these areas interact with each other not only at the level of the medulla but also through pathways projected to bulbar and spinal motor neurons.[11] The present study provides no direct evidence that the different responses of PN and HN activities to changes in depth of halothane anesthesia are attributable to the different influences of the specific medullary respiratory neurons and their efferent projections.

The differential responses may be associated with the fact that hypoglossal motoneurons lie in the medulla, whereas phrenic motoneurons are in the spinal cord. There may be differences in the recruitment or rate of discharge of neurons in both PN and HN activities with changes in anesthetic depth. In any case, the neural pathway to HN is much more vulnerable to the depressant effects of halothane anesthesia than is the neural pathway to PN.

The changes in the two nerves' activities in response to increasing depths of halothane anesthesia do not preclude possible anesthetic effects at the neuromuscular junction or on the muscles themselves that might result in alterations in muscle activity. For example, halothane

was found to have weak neuromuscular blocking properties, which has been attributed to its effect on the muscle membrane raising the threshold at which an end-plate potential is propagated.[12] A possible presynaptic effect on halothane causing a reduced release of acetylcholine also has been described.[13] Although assessment of changes in overall respiratory muscle function requires the understanding of the effects of halothane on the peripheral neuromuscular system in different muscle groups, variations in sensitivity of the peripheral neuromuscular system in different respiratory muscles have not been investigated fully.

In the present study we also examined the transient changes in respiratory activity of both PN and HN following a sudden increase in anesthetic depth with various agents. Although this procedure does not permit a detailed analysis of dose-related effects of anesthetics, it can show the time course of changes in both nerves' activity. The results showed that, compared with PN activity, HN activity was depressed preferentially following administration of halothane, thiopental, and diazepam, whereas ketamine did not cause such differential suppression. These results suggest that the differential suppression of PN and HN may be associated not only with the depth of anesthesia but also with the type of anesthetic used. Our findings are in agreement with the commonplace clinical observations that deepening anesthesia with halothane, thiopental, and diazepam causes the preferential relaxation of the tongue, leading frequently to pharyngeal obstruction, whereas the airway is better preserved with ketamine than with other anesthetics. However, more dose–response data for each anesthetic definitely are needed in order to clarify whether the response to ketamine is truly different than that to other anesthetics.

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