Different Laryngeal Responses during Respiratory Arrest Produced by Hypoxia Withdrawal, Thiopentone, Ketamine, and Lidocaine in Cats

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The changes in laryngeal resistance (L_R) during respiratory arrest produced by withdrawal of hypoxia stimulation and administration of various respiratory depressants were studied in 14 spontaneously breathing, anesthetized cats (11 cats with α-chloralose and three cats with halothane). Withdrawal of hypoxia stimulation caused a transient respiratory arrest with no central inspiratory activity, during which a considerable increase in L_R was observed to a level higher than the fixed resistance after muscle paralysis [$L_{R(fix)}$]. Intravenous injection of thiopentone, ketamine, and lidocaine all caused a transient respiratory arrest. However, the effects on the laryngeal function and the central inspiratory activity were different for each agent. Both thiopentone and ketamine induced an inspiratory apneusis pattern in phrenic nerve discharge, and lidocaine caused a silence of phrenic nerve activity. Thiopentone relaxed the larynx, and L_R during thiopentone-induced respiratory arrest was almost equal to $L_{R(fix)}$. Ketamine maintained a dilatation of the larynx, and L_R during ketamine-induced respiratory arrest was lower than $L_{R(fix)}$. Lidocaine caused a constriction of the larynx and L_R greatly increased, leading frequently to laryngospasm. These results indicate that hypoxia withdrawal, thiopentone, ketamine, and lidocaine all cause different effects on the central inspiratory activity, and that the central respiratory depression produced by these methods is not accompanied by a uniform depression of laryngeal function. (Key words: Anesthetics, intravenous: ketamine; thiopental. Anesthetics, local: lidocaine. Hypoxia. Larynx.)

THE LARYNGEAL MUSCLES contract with phasic respiratory rhythms and their fine control of the vocal cords produces rapid changes in laryngeal resistance (L_R) within the respiratory cycle. It has been observed that when ventilation is stimulated by hypoxia or hypercapnia, the size of the laryngeal channel is increased and the laryngeal airflow resistance is decreased, whereas hypocapnia leads to a decrease in size of the laryngeal channel and an increase in resistance to flow.[1,2] These observations suggest that the laryngeal caliber is controlled by a central mechanism closely related with respiratory activity. Thus, it is expected that respiratory depression produced by a respiratory depressant would cause concurrent depression of laryngeal function. However, little is known about direct effects of respiratory depressants on laryngeal function. In the course of experiments studying the effects of respiratory depressants on laryngeal function, it was noticed that different respiratory depressants caused different laryngeal responses. This report describes characteristic changes in laryngeal airflow resistance during respiratory arrest induced by several respiratory depressants.

Methods

Experiments were performed on 14 adult cats weighing 2.0–4.0 kg. Eleven of 14 cats were anesthetized first with halothane and then with α-chloralose (40 mg/kg) intravenously. The right femoral artery was catheterized for the measurement of arterial pressure (AP) and the withdrawal of arterial blood samples. A catheter was inserted into the inferior vena cava from the right femoral vein. Each cat was tracheostomized with a cannula tied into the lower cervical trachea and directed caudally. A second cannula was tied in the upper part of the trachea and was directed rostrally, care being taken to avoid damaging the recurrent laryngeal nerves. The pharynx was opened widely in the midline and the epiglottis was gently pulled ventrally with a suture or was removed surgically, thus permitting direct visualization of the movement of the vocal cords. A constant stream of humidified warm air was passed rostrally through the upper cannula at a constant rate of 2–4 l/min ($1.0 \, l \cdot min^{-1} \cdot kg^{-1}$). Pressure upstream from the larynx (the upper tracheal pressure: P_{UT}) was measured with a pressure transducer and the ratio of P_{UT} to the laryngeal flow was taken as laryngeal resistance (L_R). Tidal volume and respiratory airflow were measured with a pneumotachograph attached to the lower tracheal cannula. End-tidal CO_2 PET_{CO_2} was measured using an infrared CO_2 analyzer. A phrenic nerve root was isolated and prepared for recording of its discharge by a preamplifier-amplifier system. All of the variables were recorded on ultraviolet-sensitive paper. Further details of these methods are given elsewhere.[3,4] After the surgical preparation of the animal, halothane was discontinued and 30–40 min were allowed to achieve a control state while the animal was breathing 100 per cent O_2. Rectal temperature was monitored and maintained at 37–38° C by means of a heat lamp.

TABLE 1. Values* of Inspiratory Resistance (L_{RI}) and Expiratory Resistance (L_{RE}) Under Stable States (Values are in cm $H_2O \cdot 1^{-1} \cdot s$)

Cat Number	Control		Before Thiopentone		Before Ketamine		Before Lidocaine		L_{RI}		L_{RE}	
	L_{RI}	L_{RE}	L_{RI}	L_{RE}	L_{RI}	L_{RE}	L_{RI}	L_{RE}	Mean ± SD	SD/Mean	Mean ± SD	SD/Mean
1	2.65	3.53	2.65	3.53	2.47	3.71	2.82	3.35	2.65 ± 0.14	0.05	3.53 ± 0.15	0.04
2	6.45	10.05	6.30	9.90	6.75	10.20	6.60	10.35	6.53 ± 0.19	0.03	10.13 ± 0.19	0.02
3	12.00	13.95	12.30	14.10	12.60	14.25	11.55	13.50	12.11 ± 0.45	0.04	13.95 ± 0.32	0.02
4	18.00	24.90	18.00	24.90	17.10	24.00	18.60	25.50	17.93 ± 0.62	0.03	24.83 ± 0.62	0.02
5	5.85	6.92	5.69	7.08	5.85	6.92	6.15	6.62	5.89 ± 0.19	0.03	6.89 ± 0.19	0.03
6	12.00	16.00	11.60	16.80	11.60	15.20	12.20	15.60	11.85 ± 0.30	0.03	15.90 ± 0.68	0.04
7	2.55	3.00	2.55	3.00	2.25	2.85	2.70	3.30	2.51 ± 0.19	0.08	3.04 ± 0.19	0.06
8	4.36	5.09	4.00	5.27	4.36	4.91	4.73	5.27	4.36 ± 0.30	0.07	5.14 ± 0.17	0.03
9	6.51	8.57	6.34	8.06	6.86	8.06	6.86	8.91	6.64 ± 0.26	0.04	8.40 ± 0.42	0.05
10	5.44	6.00	5.81	6.56	5.81	6.38	5.06	6.00	5.53 ± 0.36	0.06	6.24 ± 0.28	0.05
11	8.00	20.00	7.80	18.00	8.40	18.00	8.00	22.00	8.05 ± 0.25	0.03	19.50 ± 1.91	0.10
MEAN	7.62	10.73	7.55	10.65	7.64	10.41	7.75	10.95				
±SD	4.67	7.14	4.68	6.94	4.53	6.68	4.72	7.47				

* All the values were obtained while the animals were breathing 100 per cent O_2.

In order to cause a transient respiratory arrest, either the sudden withdrawal of hypoxia stimulation or the rapid injection of a respiratory depressant (4 mg/kg thiopentone; 3 mg/kg ketamine; 2 mg/kg lidocaine) was performed, and the maximum L_R during respiratory arrest was calculated from the values of P_{UT} and the corresponding laryngeal airflow in each animal. The sudden withdrawal of hypoxia stimulation was accomplished by administering 100 per cent O_2 into the inspired line after the animal had breathed a hypoxic gas mixture (9 per cent O_2 in N_2) for 5 min. Intravenous respiratory depressants were given while the animal was breathing 100 per cent O_2. Although the withdrawal of hypoxia stimulation was always performed first, random order was followed for the administration of intravenous agents. In order to minimize the residual effects of previously injected agents in each animal, sufficient time (usually 30–60 min) elapsed before the administration of the next agent to allow ventilation, PE'_{CO_2}, P_{UT}, and arterial pressure to return to approximately the control levels. Arterial blood P_{O_2}, P_{CO_2}, and pH were measured at various times during the experiments.

In some animals, an intra-arterial catheter was advanced via the left femoral artery to the ascending aorta and intra-arterial injection of lidocaine (0.5 mg/kg) was performed.

After the above procedures, the animal was paralysed with pancronium bromide (0.1 mg/kg) and laryngeal resistance with the vocal cords in the completely relaxed position [the fixed resistance after muscle paralysis: $L_{R(fix)}$] was determined.

In another three cats, anesthesia was induced and maintained with halothane (1.5 per cent inspired concentration) in order to examine the possible effects of different background anesthesia on laryngeal responses to various respiratory depressants. In these experiments

FIG. 1. Effects of withdrawal of hypoxia stimulation on respiration and laryngeal resistance. Immediately following sudden administration of 100 per cent O_2 (at arrow) the animal stopped ventilation with silence of phrenic nerve activity. The upper tracheal pressure (P_{UT}) increased during respiratory arrest. (IPNA: integrated phrenic nerve activity; PNA: phrenic nerve activity.)
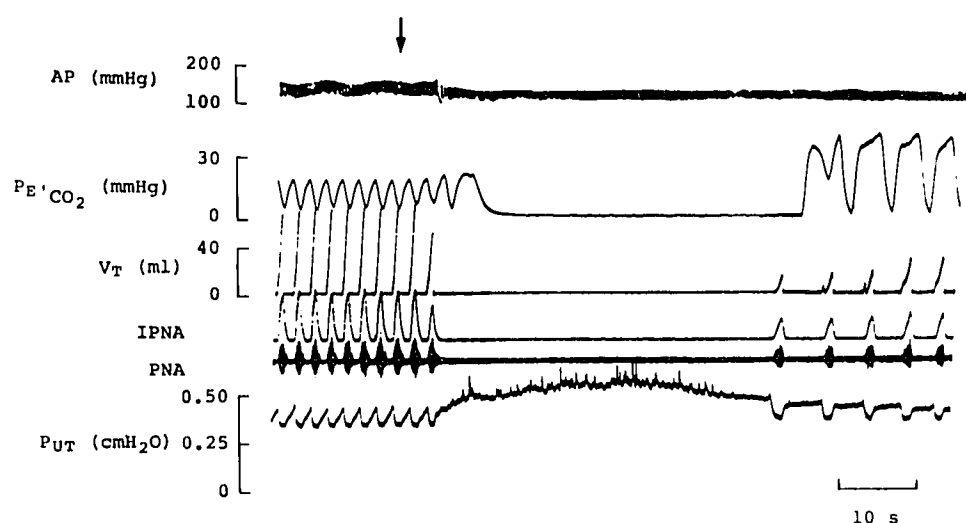
TABLE 2. The Values of L_R during the Control State and the Maximum L_R during Respiratory Arrest Produced by Hypoxia Withdrawal, Thiopentone, Ketamine, and Lidocaine (Values are in cm $H_2O \cdot l^{-1} \cdot s$)

Cat Number	$L_{RI(cont)}$	$L_{RE(cont)}$	Thiopentone	Ketamine	Lidocaine (iv)	Lidocaine (ia)	Hypoxic Withdrawal	$L_{R(fix)}$
1	2.65	3.53	3.53	2.65	>46.40*		4.94	3.53
2	6.54	10.05	11.25	6.75	>60.00*	>60.00*	13.05	10.95
3	12.00	13.95	14.55	12.75	37.50	36.00	22.50	15.00
4	18.00	24.90	24.00	18.00	>39.90*		33.00	27.00
5	5.85	6.92	7.69	5.85	>30.77*		9.23	7.69
6	12.00	16.00	15.00	13.00	>32.00*		18.00	16.00
7	2.55	3.00	3.00	2.70	18.00	22.50	3.30	3.00
8	4.36	5.09	4.91	4.55	10.90		5.45	5.09
9	6.51	8.57	9.09	6.86	>34.29*		10.29	9.43
10	5.44	6.00	6.56	5.63	>37.50*		11.25	6.19
11	8.00	20.00	19.20	7.00	>84.00*		26.00	22.00
MEAN	7.62†	10.73	10.80	7.77†			14.27‡	11.44
±SD	4.67	7.14	6.75	4.83			9.52	7.79

* Laryngospasm with saturation of pressure recorder.

† $P < 0.05$, ‡ $P < 0.01$ [significantly different from values of $L_{R(fix)}$ by Student's paired t test].

$L_{RI(cont)}$: inspiratory laryngeal resistance during control state.
$L_{RE(cont)}$: expiratory laryngeal resistance during control state.

the protocol was basically the same as the experiments with α-chloralose anesthesia. Statistical analysis was performed using Student's paired t test when appropriate.

FIG. 2. Changes in respiration and laryngeal resistance following intravenous injection (at arrow) of thiopentone (*A*) and ketamine (*B*) obtained in a spontaneously breathing animal. Note that phrenic nerve discharge continued during respiratory arrest in both cases.

Results

STABILITY OF THE PREPARATION

Although four to five hours were required to perform the complete study for each animal, responses of L_R were consistent and reproducible, and L_R returned to the control value within 20–40 min after administration of each respiratory depressant. Values of L_R before the administration of each respiratory depressant are listed in table 1.

HYPOXIA WITHDRAWAL

After inhalation of the hypoxic gas mixture for 5 min, the values of Pa_{O_2} and Pa_{CO_2} were 60 ± 4 (mean ± SD) and 21 ± 2 mmHg, respectively. Figure 1 shows an example of hypoxia withdrawal. During hypoxia, P_{UT} changes cyclically, increasing during the expiratory phase and decreasing during the inspiratory phase. With sudden administration of 100 per cent O_2 hypoxia stimulation was withdrawn and ventilation of the animal was arrested for about 40 s until Pa_{CO_2} attained the threshold for inspiration. During this respiratory arrest, no phrenic activity was observed. P_{UT} increased considerably during respiratory arrest, indicating an increase in L_R.

Similar results were obtained in all the animals anesthetized with α-chloralose and the maximum L_R during respiratory arrest was always higher than $L_{R(fix)}$ ($P < 0.01$) (table 2).

INJECTION OF RESPIRATORY DEPRESSANTS

Although intravenous injections of thiopentone, ketamine, and lidocaine all caused an immediate and transient respiratory arrest which lasted for 5 to 30 s in all the animals, effects on central respiratory activity and
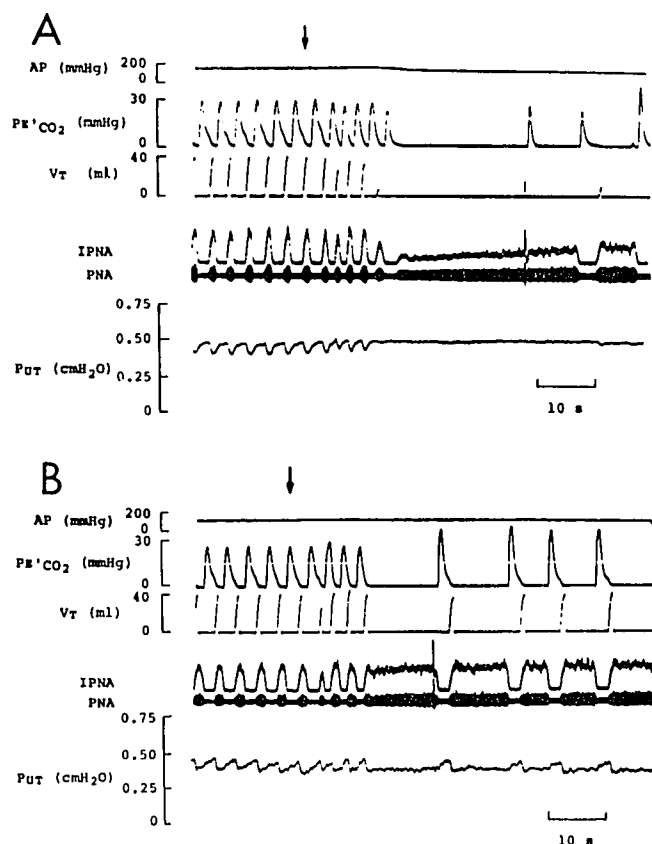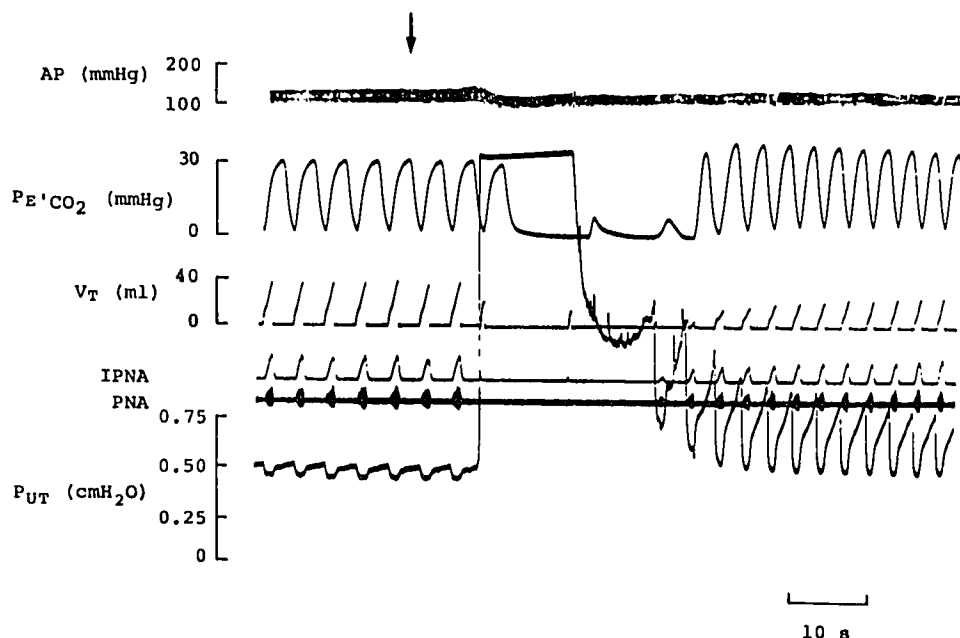
FIG. 3. Effects of intravenous lidocaine on respiration and laryngeal resistance. Following administration of lidocaine (at arrow) laryngospasm accompanied by apnea occurred. Note the sudden and very large increase in the upper tracheal pressure with saturation of pressure recorder.

on laryngeal function differed from one agent to another. Figure 2 shows examples of responses of respiration and laryngeal function to intravenous thiopentone (fig. 2A) and ketamine (fig. 2B) observed in most of the animals. Both thiopentone and ketamine caused a cessation of respiratory movement immediately following the injection. However, the phrenic nerve continued to fire (inspriatory apneusis pattern) during respiratory arrest, indicating that cessation of ventilation is not the same as the cessation of central inspriatory activity. It can be also noticed that the height of integrated phrenic nerve activity during ketamine-induced respiratory arrest was comparable to that of the pre-injection period, whereas the height of integrated phrenic nerve activity during thiopentone-induced respiratory arrest was much lower than that of the preinjection period. The effect of ketamine on laryngeal function was also different from that of thiopentone. As listed in table 2, L_R during ketamine-induced respiratory arrest was always lower than $L_{R(fix)}$ ($P < 0.05$), whereas L_R during thiopentone-induced respiratory arrest was almost equal to $L_{R(fix)}$.

The effects of intravenous lidocaine on central inspiratory activity and on laryngeal function were remarkably different from those produced by ketamine and thiopentone. In all the animals, there was a very large increaese in L_R with a transient respiratory arrest 5–10 s after the injection of lidocaine. Unlike thiopentone and ketamine, no continuous phrenic discharge was observed during lidocaine-induced respiratory arrest. In eight of 11 cats anesthetized with α-chloralose, by directly watching the movement of the vocal cords, we observed that lidocaine caused a prolonged tight closure of the vocal cords, which can be defined clinically as laryngospasm.

An example of this lidocaine-induced laryngospasm is shown in figure 3.

In three animals, in addition to the intravenous injection, an intra-arterial injection of lidocaine was given. Although a typical laryngospasm was observed in only one animal, there was consistently a large increase in L_R immediately following the injection (table 2).

Effects of Different Background Anesthesia on Laryngeal Responses

Because of the possibility that an interaction between α-chloralose (background anesthetic) and the test respiratory depressants might have caused the particular results, halothane was used as the background anesthetic in three animals. With halothane anesthesia, the effects on laryngeal function and on central inspiratory activity of the various respiratory depressants were qualitatively similar to those observed with α-chloralose anesthesia. Figure 4 shows an example of laryngeal responses to various respiratory depressants obtained in one of the animals anesthetized with halothane. The values of L_R following administration of the test drugs during halothane anesthesia are listed in table 3.

Discussion

We have demonstrated that a sudden decrease in respiratory activity induced by either withdrawal of hypoxia stimulation or administration of various respiratory depressants causes immediate laryngeal responses. However, the responses induced by these procedures were by no means uniform even in the presence of the same degree of respiratory depression. The observed ef-
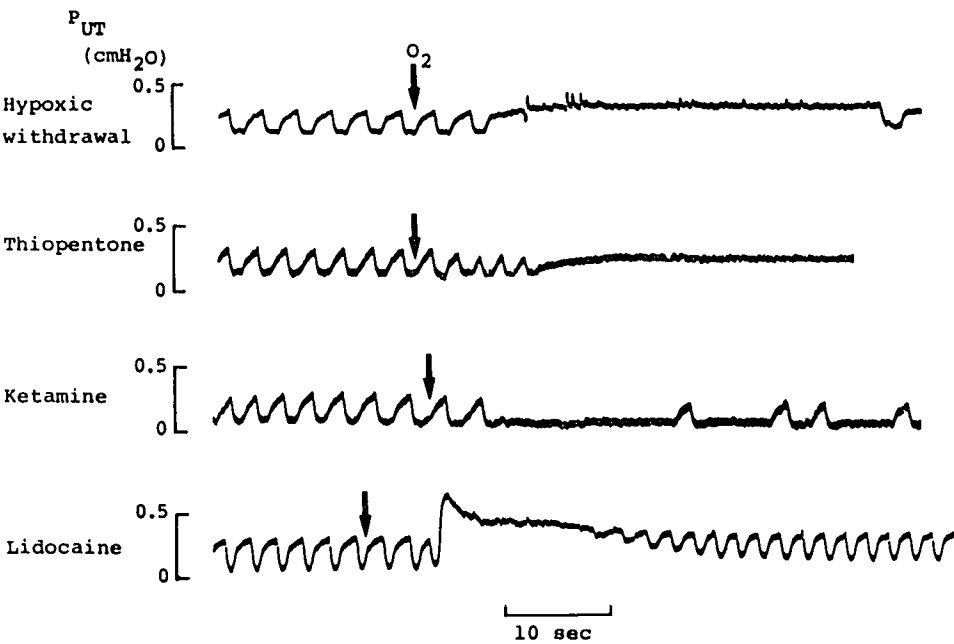
FIG. 4. Changes in laryngeal resistance following administration (at arrow) of various respiratory depressants during halothane anesthesia.

fects of a test respiratory depressant may have been modulated by interaction with the background anesthetic or with other drugs used. However, the effects of a given respiratory depressant was consistent whether the background anesthetic was α-chloralose or halothane and regardless of what other test respiratory depressants had been administered. Therefore, the observed changes can be related primarily to the action of the respiratory depressant under consideration. Thus, L_R during respiratory arrest induced by thiopentone was almost equal to $L_{R(fix)}$, indicating that neither constriction nor dilatation of the larynx occurred. L_R during ketamine-induced respiratory arrest, on the other hand, was always lower than $L_{R(fix)}$, indicating that the larynx was kept dilated during respiratory arrest. It has been shown that both pentobarbital and ketamine frequently cause respiratory arrest by inducing respiratory apneusis.[5,6] Although the recordings from the phrenic nerve in our study confirmed that both thiopentone and ketamine induce an apneusis

pattern, it was also noticed that ketmine caused little or no effect on the peak height of phrenic nerve activity during inspiratory apneusis, whereas thiopentone reduced it considerably.

If it is assumed that inspiratory activity activates the adductor muscles and dilates the larynx even during inspiratory apneusis, the different effects on the central inspiratory activity of ketamine and thiopentone may explain the difference between the laryngeal responses to ketamine and thiopentone observed in this study.

A sudden withdrawal of hypoxia stimulation caused respiratory arrest with no inspiratory activity. In this case, L_R during respiratory arrest was much higher than $L_{R(fix)}$. This indicates that adductor muscles of the larynx were activated and constriction of the larynx occurred. This observation is in accordance with previous reports[1,4] that a decrease in Pa_{CO_2} progressively increases laryngeal resistance. The constriction of the larynx may possibly be attributed to both the absence of the central inspiratory

TABLE 3. The Values of L_R during Control State and the Maximum L_R Following Administration of Various Respiratory Depressants under Halothane Anesthesia (cm $H_2O \cdot l^{-1} \cdot s$)

Cat Number	$L_{RI(cont)}$	$L_{RE(cont)}$	Thiopentone	Ketamine	Hypoxic Withdrawal	Lidocaine	$L_{R(fix)}$
12	2.70	4.50	4.50	2.70	6.00	8.55	4.50
13	6.86	10.29	10.29	6.51	12.00	17.14	11.14
14	1.88	5.63	5.63	2.06	7.50	15.00	6.19
MEAN	3.81	6.81	6.81	3.76	8.50	13.56	7.28
±SD	2.67	3.07	3.07	2.41	3.12	4.47	3.45

activity which activates the abductor muscles and the direct effect of hypocapnia on a central mechanism regulating the laryngeal closure reflex.[4]

Of the responses to the depressants, the one produced by administration of lidocaine is the most surprising. Since it is known that intravenous lidocaine considerably depresses both pharyngeal and laryngeal reflexes[7-9] it was unexpected that lidocaine would greatly increase L_R. We used a dose equivalent to that used clinically in the treatment of cardiac arrhythmia. Although the speed of injection was quite fast and the concentration of lidocaine in blood was considered to be very high, no toxic effects such as convulsions or hypotension were observed. In this study, we did not investigate either the precise site of action or mechanisms of laryngeal constriction induced by lidocaine. However, the observation that intra-arterial injection of lidocaine greatly increased L_R as well suggests that direct stimulation of the central nervous system by lidocaine is a possible mechanism of lidocaine-induced constriction of the larynx. In this context, it is worthy to note that a subconvulsive dose of lidocaine can produce an excitatory action upon various areas of the brain, particularly the amygdala complex[10] which is known to have a close relation with the upper tracheal reflex.[11]

Although simple extrapolation of our results to the clinical situation may not be entirely valid, our findings emphasize the complexity of the interrelationships between laryngeal function and central respiratory activity.

Our findings imply that changes in laryngeal caliber are not simply accompaniments of changes in central respiratory activity.

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