

Effect of Halothane on Diaphragmatic Muscle Function in Pentobarbital-anesthetized Dogs

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The mechanism underlying the decrease in minute ventilation (\dot{V}_E) observed under halothane anesthesia was investigated in nine spontaneously breathing dogs. Anesthesia was induced with pentobarbital sodium and was maintained with halothane. Inspired fraction of halothane (F_{Ihal}) was increased every 30 min, from 0.005 to 0.02. \dot{V}_E decreased from 8.1 ± 0.9 to 4.8 ± 0.4 l · min⁻¹ ($P < 0.001$), as F_{Ihal} increased from 0 to 0.02. This resulted from a decrease in both mean inspiratory flow (V_T/T_I) and the duty ratio (T_I/T_{TOT}). Transdiaphragmatic pressure (Pdi) and the integrated electrical activity of both hemidiaphragms (Edi) were measured during normal breathing, and during breathing against closed airways (P^0di , E^0di), in order to obtain an index of the inspiratory neuromuscular output of the diaphragm. With increasing F_{Ihal} , there was a significant decrease in Pdi, P^0di , Edi, and E^0di . The authors measured Pdi and Edi generated during supramaximal stimulation of the two phrenic nerves (P^Sdi , E^Sdi) at frequencies of 10, 20, 50, and 100 Hz, in order to eliminate in this decrease the role played by a decrease in the neural drive to breathing. P^Sdi and E^Sdi decreased significantly with increasing F_{Ihal} , and had not returned to the control values 30 min after discontinuation of halothane administration. The authors conclude that, in pentobarbital-anesthetized dogs, halothane is responsible for a diaphragmatic dysfunction, which may be located either at the neuromuscular junction, on the contractile processes of the muscle, or on both, and for a decrease in the activation time of the inspiratory muscles. Both of these effects contribute to the decrease in \dot{V}_E observed under halothane anesthesia. (Key words: Anesthetics, volatile: halothane. Muscle: skeletal, diaphragm. Neuromuscular junction. Ventilation: pattern of breathing.)

HALOTHANE HAS BEEN KNOWN for years to decrease minute ventilation (\dot{V}_E).¹ This action generally is attributed to a direct effect of the drug on the central nervous system (CNS).² However, although \dot{V}_E depends on CNS activity, it also depends on respiratory muscle contractility, which will transform central respiratory drive into pressure, and on respiratory mechanics, which will determine the geometry of the respiratory system and the changes in lung volume resulting from a given muscle contraction.

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A previous report has shown that halothane decreases occlusion pressure, an index of the neuromuscular drive to breathing, and that a major component of the halothane-induced ventilatory depression resulted from the peripheral suppression of intercostal muscle function.³ It has also been shown, in *in vitro* experiments, that halothane depresses both neuromuscular transmission and the contractile mechanisms of muscular contraction.⁴⁻⁷ Therefore, the purpose of this study was to determine, in an *in vivo* preparation, the effect of halothane anesthesia on diaphragmatic muscle function.

Methods

ANIMALS

Nine healthy, mongrel dogs, weighing between 18 and 25 kg, were anesthetized with iv pentobarbital sodium (25 mg · kg⁻¹). The animals were intubated with a cuffed endotracheal tube (N^o9) and mechanically ventilated during the surgical procedure. The right femoral artery was cannulated to monitor blood pressure. Rectal temperature was monitored continuously with a thermistor and maintained constant. All dogs were studied in the supine position.

RESPIRATORY VARIABLES

The dogs were breathing through a Hans-Rudolph[®] valve. Flow rate was obtained with a Fleish[®] pneumotachograph and a Validyne MP 45 differential pressure transducer (Validyne Co., Northridge, CA). The integrated flow signal was used to determine tidal volume. Inspiratory (T_I), expiratory (T_E), and total (T_{TOT}) times of the breathing cycle were measured from the flow signal. Transdiaphragmatic pressure (Pdi), which is defined as gastric pressure minus pleural pressure, was measured by means of two thin-wall, latex balloons (5 cm in length), one positioned in the stomach and the other in the middle third of the esophagus.⁸⁻¹⁰ The gastric balloon was connected to one side of a DP 15 Validyne differential transducer by means of a polyethylene catheter (ID 1.4 mm, ED 2 mm). The esophageal balloon was connected by similar means, and a Y tube to the opposite side of the transducer and to another transducer, receiving an input

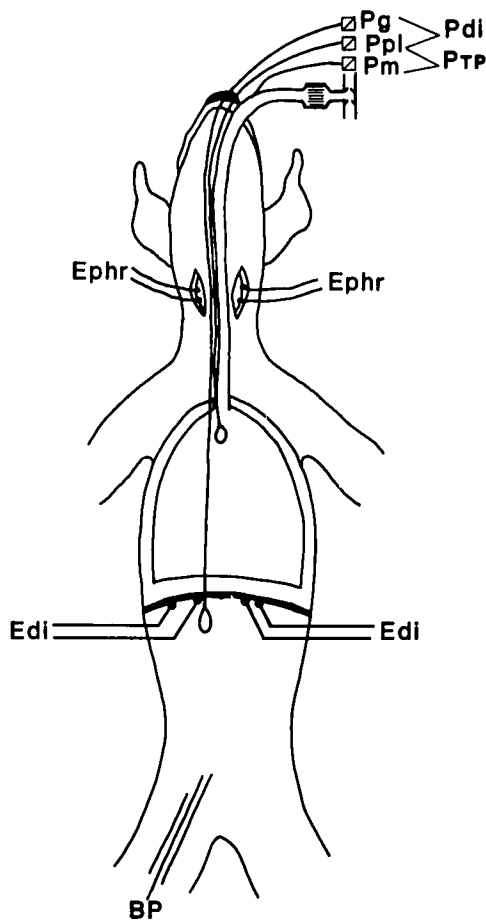


FIG. 1. Animal preparation. Dogs breathed pure oxygen spontaneously. Transdiaphragmatic pressure (Pdi) was measured with two balloons, as the difference between gastric (Pg) and esophageal pressure (Ppl). Transpulmonary pressure (P_{TP}) was the difference between Ppl and mouth pressure (Pm). A catheter was inserted in the femoral artery to monitor blood pressure (BP). Electrodes were placed around the phrenic nerves (Ephr) and in the diaphragmatic muscle (Edi).

from the mouth pressure (P_{ao}). The first transducer measured gastric pressure relative to body surface pressure, the second recorded Pdi, and the third measured transpulmonary pressure (P_{TP}), defined as the difference between P_{ao} and esophageal pressure. Airway occlusions at functional residual capacity (FRC) were performed repeatedly throughout the experiment. The mouth occlusion pressure that developed during the occluded inspiration (P_{ao}^0) also was measured from the third transducer, the pleural pressure being temporarily disconnected. P_{ao}^0 and the Pdi occlusion pressure (P_{di}^0) were measured 200 ms after the onset of the occluded inspiration.

DIAPHRAGMATIC MUSCLE CONTRACTION

The contractile properties of the diaphragm were quantified by measuring the pressure (P^{Sdi}) that it gen-

erates at different frequencies of stimulation (Pdi—frequency characteristics).^{9,11} Electrodes were placed around the isolated C5 roots of both phrenic nerves under mineral oil in order to stimulate the nerves. The integrated electrical activity of both hemidiaphragms (Edi) was recorded directly, as previously described.¹² Access to the muscle was obtained through a midline laparotomy incision. The electrodes were fashioned from No. 10 fish-hooks, insulated to nearly 5 mm from the tip. The electrodes were placed approximately 1 cm apart on the anterior part of the hemidiaphragm, 5 cm from the central tendon. The surgical incision then was closed in layers. The phrenic nerves were stimulated using a DISA 1 SE 06[®] stimulator. The stimulus voltage was increased progressively while the compound action potential of the diaphragm was recorded. Maximal response was judged by the size of the diaphragmatic twitches. Maximal stimulation was achieved at 8 to 10 V. The voltage then was increased 10 to 20% to ensure that stimulations remained supramaximal. Stimulations were obtained by stimuli of 0.1 ms duration during approximately 2 s, at various frequencies: 10, 20, 50, and 100 Hz.

The Pdi generated during the various conditions of stimulation depends on diaphragmatic length, which in turn depends on lung volume.¹⁰ To ensure the same initial diaphragmatic length before stimulations, the airways were occluded at FRC. The FRC at which the Pdi frequency measurements were made remained constant throughout the experiment, as demonstrated by end-expiratory P_{TP} . The electrical activity of both hemidiaphragms during the phrenic nerve stimulations was monitored continuously. A schematic representation of the experimental design is shown in figure 1.

EXPERIMENTAL PROCEDURES

All animals breathed 100% oxygen. Ventilatory variables and blood pressure were measured, and single twitch stimulations and the Pdi frequency curves were performed after 1 h of spontaneous quiet breathing to establish control values. All signals were recorded on an ALCO EN 68[®] strip-chart recorder, using a paper speed of 100 mm/s during single twitch stimulations, of 25 mm/s during the occlusion pressure measurement, and of 10 mm/s during the other periods. Halothane then was added to the inhaled oxygen by a continuous flow Cyprane Mark 3[®] vaporizer previously calibrated. The dial of the vaporizer was set to 0.5%. All the measurements were repeated 60 min later. Thereafter, the dial of the vaporizer was changed to 1%, 1.5%, and 2%, and all of the measurements were performed 30 min after each setting change. Arterial blood gas measurements were made before each measurement. In two dogs, a ventilatory arrest

TABLE 1. Results of the Different Ventilatory Variables with Increasing Levels of F_I hal, and 30 min after Halothane Discontinuation

	Control (n = 9)	0.005 F_I hal (n = 9)	0.01 F_I hal (n = 9)	0.015 F_I hal (n = 7)	0.02 F_I hal (n = 5)	30 Min Recovery (n = 7)
\dot{V}_E (l · min ⁻¹)	8.1 ± 0.9	5.9 ± 0.4*	5.3 ± 0.5†	5.2 ± 0.5†	4.8 ± 0.4†	10.1 ± 3.6
P_{aCO_2} (mmHg)	36.9 ± 2.9	42.0 ± 4.3*	55.6 ± 4.5†	65.0 ± 5.7†	75.3 ± 6.0†	44.0 ± 4.4
V_T (ml)	213 ± 34	157 ± 13	137 ± 15†	130 ± 13†	125 ± 16†	197 ± 27
f (c · min ⁻¹)	39.0 ± 4.0	34.1 ± 4.7	36.3 ± 4.9	40.0 ± 3.6	37.2 ± 2.8	51.0 ± 10.4
V_T/T_I (ml · s ⁻¹)	307 ± 46	225 ± 26‡	210 ± 29*	236 ± 23*	245 ± 20*	367 ± 95
T_I/T_{TOT}	0.48 ± 0.03	0.40 ± 0.02*	0.38 ± 0.01†	0.35 ± 0.01†	0.33 ± 0.03†	0.51 ± 0.04
P_{ao}^0 (cmH ₂ O)	7.6 ± 1.2	5.9 ± 0.9‡	5.3 ± 0.9*	6.1 ± 1.1‡	5.9 ± 0.9‡	10.4 ± 2.7

* $P < 0.01$, † $P < 0.001$, ‡ $P < 0.05$ when compared with control values.

was observed at 0.015 inspired fraction of halothane (F_I hal), and at 0.02 F_I hal in another two dogs. In all dogs, blood pressure was maintained within 30% of the control values by the infusion of a colloid solution, which amounted to 250 ml in two dogs. In seven dogs, all measurements were repeated 30 min after disconnection of the vaporizer to determine the recovery profile.

All values given are means ± SEM. Statistical analysis was performed using analysis of variance. Data were considered significantly different if $P < 0.05$.

Results

The administration of halothane induced a dose-dependent ventilatory depression. The results of the different ventilatory variables are shown in table 1. The decrease in \dot{V}_E was associated with a marked increase in P_{aCO_2} . The decrease in \dot{V}_E was due to a significant decrease in tidal volume (V_T) without any significant change in respiratory frequency (f).

Minute ventilation also can be expressed as the product of mean inspiratory flow (V_T/T_I) and the duty ratio (T_I/T_{TOT}).¹³ Halothane administration resulted in a decrease in these two variables. The decrease in T_I/T_{TOT} resulted from a shortening of T_I and a mild and insignificant lengthening of T_E . T_I decreased from a control value of 0.77 ± 0.08 s to 0.72 ± 0.11 s (NS) and 0.53 ± 0.04 ($P < 0.02$) at 0.01 and 0.02 F_I hal, respectively.

Mouth occlusion pressure (P_{ao}^0) decreased significantly during halothane administration. A good correlation existed between changes in V_T/T_I and P_{ao}^0 ($r = 0.846$; $P < 0.001$). The "effective" impedance of the respiratory system, which is the ratio $P_{ao}^0/(V_T/T_I)$,¹⁴ remained unchanged during halothane inhalation, from a control value

of 0.030 ± 0.005 cmH₂O · s · ml⁻¹ to 0.029 ± 0.005 cmH₂O · s · ml⁻¹ and 0.024 ± 0.004 cmH₂O · s · ml⁻¹ at 0.01 and 0.02 F_I hal, respectively.

Diaphragmatic muscle activity during spontaneous breathing also was decreased under halothane anesthesia. P_{di} , P_{ai}^0 , E_{di} , and the integrated EMG of the diaphragm during an occluded inspiration (E^0_{di}) were significantly decreased (table 2).

The results of P^S_{di} and E^S_{di} observed during tetanic stimulations of the phrenic nerve are shown in table 3 and figures 2 and 3. With increasing F_I hal, there was a decrease in P^S_{di} , which was significant even for low frequencies of stimulation. This decrease in P^S_{di} was associated with a parallel decrease in E^S_{di} (figs. 2 and 3).

In seven dogs, the ventilatory variables were analyzed 30 min after discontinuation of halothane administration. There was a moderate ventilatory stimulation (table 1). However, none of these changes were significant due to the great variability of the results. This mild change in \dot{V}_E was achieved in spite of incomplete recovery of the phrenic-diaphragm function. For 20, 50, and 100 Hz frequencies of phrenic nerve stimulation, a 10 to 20% decrease in P_{di} remained.

Discussion

The results of this study demonstrate that different mechanisms contribute to the halothane-induced decrease in minute ventilation. A direct central effect of halothane on the inspiratory centers previously had been suggested.² Recent experiments in cats have confirmed that halothane depresses the activity of both the phrenic nerve¹⁵ and the inspiratory neurons of the solitary tract nucleus¹⁶ when end-tidal PCO_2 was maintained constant. Halothane also

TABLE 2. Results of Pressure and EMG Indices of Diaphragmatic Function with Increasing Levels of F_Ihal, and 30 Min after Halothane Discontinuation

	Control (n = 9)	0.005 F _I hal (n = 9)	0.01 F _I hal (n = 9)	0.015 F _I hal (n = 7)	0.02 F _I hal (n = 5)	30 Min Recovery (n = 7)
P _{di} cmH ₂ O	8.3 ± 1.6	6.3 ± 1.2*	5.2 ± 0.9†	5.4 ± 0.8†	4.7 ± 1.2‡	6.9 ± 1.5*
P ⁰ _{di} cmH ₂ O	4.9 ± 0.7	4.1 ± 0.6*	4.2 ± 0.8*	4.0 ± 0.8*	3.5 ± 0.9†	8.8 ± 2.7
E _{di} arbitrary units	19.3 ± 3.4	14.4 ± 2.3	12.4 ± 1.0*	12.4 ± 1.3*	9.1 ± 1.8‡	17.4 ± 3.8
E ⁰ _{di} arbitrary units	21.2 ± 2.8	15.9 ± 1.8*	14.3 ± 1.0†	14.2 ± 1.1†	11.7 ± 1.5‡	26.8 ± 4.5

Measurements were performed at end-inspiration (P_{di}, E_{di}), and 200 ms after the onset of an occluded inspiration (P⁰_{di}, E⁰_{di}).

* P < 0.05, †P < 0.01, ‡P < 0.001 when compared with control values.

has been shown to exert a depressant effect on the sensitivity to carbon dioxide³ and hypoxia.¹⁷ However, in these studies, the behavior of the respiratory centers has been judged by the response of the respiratory system in terms of minute ventilation. This variable is the final product of the respiratory system and can be influenced by changes in the mechanical properties of the respiratory system, in respiratory muscle contractility, and in neuromuscular transmission.

In order to understand the mechanisms involved in the halothane-induced decrease in \dot{V}_E , the authors evaluated the effects of increasing levels of halothane anesthesia on: 1) the diaphragmatic function, by the analysis of E_{di} and P_{di} during spontaneous breathing and during phrenic nerve stimulation; 2) the occlusion pressure, an index of the neuromuscular drive to breathing; and 3) the breathing pattern, in order to appreciate the ventilatory consequences of halothane's effect on the timing mechanisms of respiration.

EFFECT ON DIAPHRAGMATIC FUNCTION

Halothane was responsible for a decrease in P_{di} and P⁰_{di}. P⁰_{di} is the response of the phrenic-diaphragm drive

to breathing. The changes in P_{di} were associated with a parallel decrease in E_{di} and, therefore, may result from a halothane effect on central inspiratory activity, on the phrenic-diaphragm function, or on both. The results obtained during phrenic nerve stimulation indicate that a decrease in diaphragmatic function was observed with increasing F_Ihal and the same neural drive. Since direct stimulation of the diaphragm was not performed in this study, it is not possible to determine whether the effect of halothane was located at the neuromuscular junction or on the contractile processes of the muscle.

The effect of halothane on the neuromuscular junction and on muscular contraction has been studied in *in vitro* preparations.^{4,5} At high concentrations of halothane, a complete block of indirect twitch response was observed through a depression of end-plate depolarization. Pollard and Millar⁴ have shown that, in rats, halothane has a depressant effect on the direct twitch response of *in vitro* phrenic-diaphragm preparations. Identical results have been noted by Waud and Waud.⁵

The effect of halothane on the phrenic-diaphragm junction has not yet been reported in an *in vivo* study. In man anesthetized with 1.25 MAC halothane, Miller *et al.* have shown that tetanic stimulation of the ulnar nerve was sustained for frequencies up to 200 Hz.¹⁸ However,

TABLE 3. Results of Transdiaphragmatic Pressure (P_{di}) Generated for Various Frequencies of Phrenic Stimulations during Control, for Increasing Levels of F_Ihal, and 30 min after Halothane Discontinuation

	P ⁰ _{di} 10 Hz (cmH ₂ O)	P ⁰ _{di} 20 Hz (cmH ₂ O)	P ⁰ _{di} 50 Hz (cmH ₂ O)	P ⁰ _{di} 100 Hz (cmH ₂ O)
Control (n = 9)	11.9 ± 1.4	21.9 ± 2.0	27.9 ± 2.6	27.9 ± 2.5
0.005 F _I hal (n = 9)	10.5 ± 1.2	21.3 ± 2.1	27.4 ± 2.6	28.3 ± 2.8
0.01 F _I hal (n = 9)	9.9 ± 1.2*	19.6 ± 2.3*	24.9 ± 2.6*	26.3 ± 2.6*
0.015 F _I hal (n = 7)	9.6 ± 0.8*	19.1 ± 1.8*	23.2 ± 2.1†	23.9 ± 2.0†
0.02 F _I hal (n = 5)	7.9 ± 1.4	15.4 ± 2.7*	18.8 ± 3.3†	19.5 ± 3.4†
Recovery (n = 7)	10.2 ± 1.4	19.2 ± 2.2*	25.3 ± 2.5*	25.5 ± 2.5†

* P < 0.05, †P < 0.01, ‡P < 0.001 when compared with control values.

these results obtained on peripheral nerve stimulation do not exclude a different effect on phrenic nerve stimulation.

In this study, inspired rather than end-tidal concentrations of halothane have been recorded. Although it may not reflect the anesthetic depth, all of the measurements were recorded 30 min after each change of the vaporizer setting in order to collect the data at a near steady state. At 0.005 F_{Ihal} , the two measurements, performed 30 min and 60 min after the onset of halothane administration, were not different.

Since the halothane-induced decrease in diaphragmatic function was observed even for low frequencies of stimulation, and since the physiologic firing frequencies of the phrenic nerve range from 5 to 30 Hz,¹⁹ this effect seems to be involved in the halothane-induced ventilatory depression. Moreover, in the presence of curare-like drugs, or if the myoneural junction or the respiratory muscles are altered by disease, this effect of halothane may result in a more pronounced ventilatory depression.

EFFECT ON NEUROMUSCULAR DRIVE

Occlusion pressure is the airway pressure that is developed after the onset of an occluded breath.^{14,20} Occlusion pressure has been shown to depend on the neural drive, on the neuromuscular transmission, and on the contractile properties of the inspiratory muscles. This variable is not influenced by changes in the mechanical properties of the respiratory system. In this study, in spite of the increase in P_{aCO_2} , P_{aO_2} was significantly decreased with increasing F_{Ihal} . This decrease can be attributed to the decrease in central neural drive,^{15,16} and to the inhibition of the intercostal motor neurons.³ The present study shows that the decrease in P_{aO_2} is also the result of a decrease in diaphragmatic function.

The pressure generated by the respiratory muscles for a given electrical muscular stimulation may differ with changes in lung volume or in the geometry of the respiratory system because of the length-tension relationship and the Laplace law.^{12,21} In this study, FRC, as assessed by the end-expiratory transpulmonary pressure, remained unchanged throughout the experiment, suggesting the same initial diaphragmatic length before its stimulation.

The lack of change in end-expiratory P_{TF} during halothane anesthesia appears to contrast with some previous reports. After halothane administration, Southorn *et al.*²² observed a 16.9% decrease in FRC in supine dogs, while after thiopental anesthesia, Lai *et al.*²³ did not show any change in FRC. However, the effect of the addition of halothane to pentobarbital anesthesia on FRC has not yet been reported in dogs. In humans, it has been shown that FRC decreases immediately after the induction of anes-

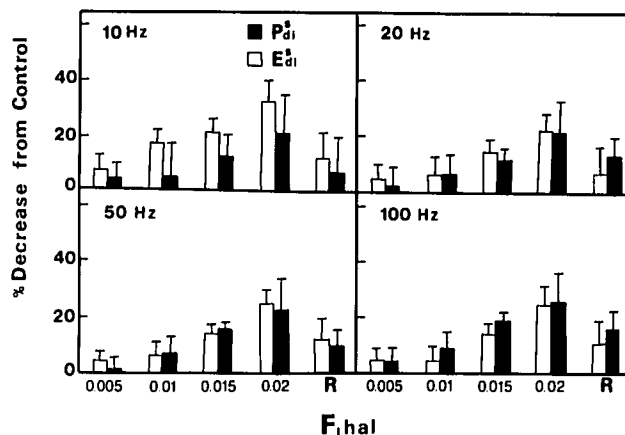


FIG. 2. Mean per cent changes in transdiaphragmatic pressure (P^S_{di}) and in electrical activity of the diaphragm (E^S_{di}) during phrenic stimulation at 10, 20, 50, and 100 Hz, with increasing fractions of inspired halothane and 30 min after halothane discontinuation (R). Bars indicate 1 SEM.

thesia with barbiturates, and remains stable thereafter, when halothane is added.²⁴

The absence of periodic inflations of the lungs can induce a decrease in FRC. Mead and Collier²⁵ have shown a decrease in pulmonary compliance, which corresponds to a 10% decrease in FRC, in thiopental-anesthetized dogs, in the absence of periodic inflations of the lungs.

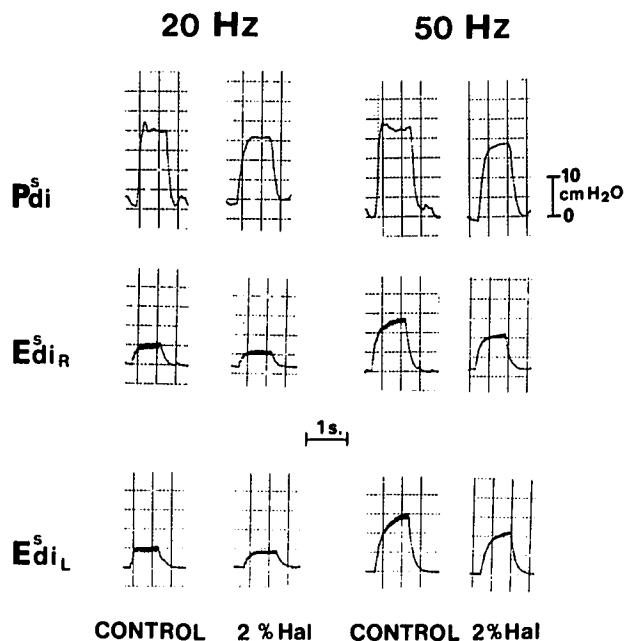


FIG. 3. Typical record of one dog showing the effects of halothane on transdiaphragmatic pressure (P^S_{di}) and on the electrical activity of the right (E^S_{diR}) and left (E^S_{diL}) hemidiaphragms at 20 and 50 Hz of supramaximal stimulation of the phrenic nerves.

However, the maximal fall of pulmonary compliance was observed during the first hour after the last lung inflations. During the following hours, the decrease in pulmonary compliance was moderate. In this study, the measurements were started at least 1 h after the onset of pentobarbital anesthesia (this delay being necessary for the preparation of the animal). The lack of change in end-expiratory P_{TP} in spite of the absence of periodic lung inflations probably is explained by the minimal changes in FRC and pulmonary compliance observed after this delay.

If it can be argued that variations in end-expiratory P_{TP} are not a sensitive index of changes in pulmonary volumes, the expected changes in FRC would not, in any case, explain our results. If halothane anesthesia and the absence of periodic lung inflations exert an effect on lung volumes, then it would be a decrease in FRC. Therefore, for an identical stimulation of phrenic nerves, $P^S di$ should be increased; however, in this study $P^S di$ was decreased. If this decrease in $P^S di$ was related to a change in the length-tension relationship of the diaphragm, it should result from an increase in FRC, which appears quite unlikely. Moreover, with such an hypothesis, it might also be difficult to explain the simultaneous decrease in $E^S di$.

V_T/T_I is the flow produced by the transformation of central inspiratory activity through the whole respiratory system. Therefore, this variable is influenced by changes in the mechanical properties of the respiratory system. Under methoxyflurane anesthesia,¹⁴ "effective" impedance of the respiratory system has been shown to be markedly increased. It was also increased during halothane anesthesia when compared with awake values.³ However, this change may be attributed to variations in the mechanical properties of the respiratory system, which occur during the induction of anesthesia, and to the added resistance due to the tracheal tube, rather than to the effect of halothane. In the present study, we observed no change in the "effective" impedance of the respiratory system when compared with control values obtained under pentobarbital anesthesia in dogs breathing through a tracheal tube.

EFFECT ON TIMING MECHANISMS

T_I/T_{TOT} is the time during which the inspiratory muscles are activated, relative to the total cycle duration. It reflects with central inspiratory drive, a second important controlling mechanism, which starts and stops inspiration.²⁶ In this study, there was a progressive and significant decrease in T_I/T_{TOT} , reaching $67.6 \pm 5.2\%$ of the control value at 0.02 F_{Ihal} . This decrease resulted from the shortening of T_I while T_E remained unchanged. In the four dogs that experienced a ventilatory arrest at 0.015

and 0.02 F_{Ihal} , T_I/T_{TOT} was continuously decreasing until the ventilatory arrest.

The decrease in the duty ratio during halothane anesthesia has already been observed. In dogs, Marsh *et al.*²⁷ noted that at 1.9 MAC halothane, the mean value of T_I/T_{TOT} was 0.259 during oxygen breathing. In the five patients reported by Tusiewicz *et al.*,³ T_I/T_{TOT} decreased during halothane anesthesia, although this decrease was less pronounced than that obtained in our study in dogs.

The effect of halothane on central timing mechanisms has been described in previous studies in an attempt to elucidate the mechanisms underlying the tachypnea observed during halothane anesthesia. Experiments in dogs²⁷ and cats^{28,29} have shown that the duration of inspiration during halothane administration is determined mainly by its action on the bulbo-pontine pacemaker mechanisms, and is little influenced by tonic vagal activity. Expiratory time during halothane administration seems to be determined by bulbo-pontine mechanisms, by vagal afferent impulses, and by peripheral chemoreceptor activity.

In this present study, we did not observe any significant increase in respiratory frequency with increasing F_{Ihal} , which usually is observed in humans. The rather elevated value for respiratory frequency during control measurements, although comparable to previous studies²⁵ and within the reported normal range,³⁰ may have influenced these results. Moreover, this effect also may be the consequence of species differences. However, the analysis of the individual values shows that, in six out of these nine dogs, we observed a progressive increase in f for lower F_{Ihal} and a decrease in f for higher F_{Ihal} , which ended in respiratory arrest for four dogs. Since within the dogs these effects were observed at different F_{Ihal} , the mean values were increased moderately and insignificantly with F_{Ihal} .

In conclusion, this study shows that different mechanisms contribute to halothane-induced respiratory depression. Halothane appears to have a dual effect on respiratory centers: decrease in central inspiratory drive and decrease in the activation time of inspiratory muscles. In addition, halothane is responsible for diaphragmatic dysfunction, which may be located either at the neuromuscular junction, on the contractile processes of the muscle, or on both, and which contributes to the decrease in \dot{V}_E observed during halothane administration. Further work is needed to determine the clinical importance of this phenomenon in man.

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