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

F. Clergue, M.D.,* N. Viñes, Ph.D., P. Lemesle, M.D.,† M. Aubier, M.D.,‡ P. Viars, M.D.,§ R. Pariente M.D.,**

The mechanism underlying the decrease in minute ventilation (\(V_E\)) 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 (\(F_{hal}\)) was increased every 30 min, from 0.005 to 0.02. \(V_E\) decreased from 8.1 ± 0.9 to 4.8 ± 0.41 · min⁻¹ (\(P < 0.001\)), as \(F_{hal}\) 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 (Pdi, E'di), in order to obtain an index of the inspiratory neuromuscular output of the diaphragm. With increasing \(F_{hal}\), there was a significant decrease in Pdi, P'di, Edi, and E'edi. The authors measured Pdi and Edi generated during supramaximal stimulation of the two phrenic nerves (P'di, E'di) 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'di and E'di decreased significantly with increasing \(F_{hal}\), 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 \(V_E\) 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 (\(V_E\)). This action generally is attributed to a direct effect of the drug on the central nervous system (CNS). However, although \(V_E\) 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.

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. It has also been shown, in vitro experiments, that halothane depresses both neuromuscular transmission and the contractile mechanisms of muscular contraction. 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 (N²9) 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. 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 by a Y tube to the opposite side of the transducer and to another transducer, receiving an input.

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erates at different frequencies of stimulation (Pdi—frequency characteristics).\textsuperscript{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.\textsuperscript{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\textsuperscript{a} 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.\textsuperscript{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 PTP. 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\textsuperscript{a} 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\textsuperscript{a} 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

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**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 (PTP) 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 (Paus). The first transducer measured gastric pressure relative to body surface pressure, the second recorded Pdi, and the third measured transpulmonary pressure (PTP), defined as the difference between Paus 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 (P0aus) also was measured from the third transducer, the pleural pressure being temporarily disconnected. P0aus and the Pdi occlusion pressure (P0d) 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 (Pd) that it generated at different frequencies of stimulation (Pdi—frequency characteristics).\textsuperscript{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.\textsuperscript{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\textsuperscript{a} 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.

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**Experimental Procedures**

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Table 1. Results of the Different Ventilatory Variables with Increasing Levels of F₁ hal, and 30 min after Halothane Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 9)</th>
<th>0.005 F₁ hal (n = 9)</th>
<th>0.01 F₁ hal (n = 9)</th>
<th>0.015 F₁ hal (n = 7)</th>
<th>0.02 F₁ hal (n = 5)</th>
<th>30 min Recovery (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}_E$ (l·min⁻¹)</td>
<td>8.1 ± 0.9</td>
<td>5.9 ± 0.4*</td>
<td>5.3 ± 0.5†</td>
<td>5.2 ± 0.5†</td>
<td>4.8 ± 0.4†</td>
<td>10.1 ± 3.6</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (mmHg)</td>
<td>36.9 ± 2.9</td>
<td>42.0 ± 4.3*</td>
<td>55.6 ± 4.5†</td>
<td>65.0 ± 5.7†</td>
<td>75.3 ± 6.0†</td>
<td>44.0 ± 4.4</td>
</tr>
<tr>
<td>$V_T$ (ml)</td>
<td>213 ± 34</td>
<td>157 ± 13</td>
<td>137 ± 15†</td>
<td>130 ± 13†</td>
<td>125 ± 16†</td>
<td>197 ± 27</td>
</tr>
<tr>
<td>$\tau$ (s·min⁻¹)</td>
<td>39.0 ± 4.0</td>
<td>34.1 ± 4.7</td>
<td>36.3 ± 4.9</td>
<td>40.0 ± 3.6</td>
<td>37.2 ± 2.8</td>
<td>51.0 ± 10.4</td>
</tr>
<tr>
<td>$V_{T1}/T_{TOT}$ (ml·s⁻¹)</td>
<td>307 ± 46</td>
<td>225 ± 26‡</td>
<td>210 ± 29*</td>
<td>236 ± 23*</td>
<td>245 ± 20‡</td>
<td>367 ± 95</td>
</tr>
<tr>
<td>$P_{aEO}$ (cmH₂O)</td>
<td>0.48 ± 0.03</td>
<td>0.40 ± 0.02*</td>
<td>0.38 ± 0.01†</td>
<td>0.35 ± 0.01†</td>
<td>0.33 ± 0.03†</td>
<td>0.51 ± 0.04</td>
</tr>
<tr>
<td>$P_{EO}$ (cmH₂O)</td>
<td>7.6 ± 1.2</td>
<td>5.9 ± 0.9‡</td>
<td>5.3 ± 0.9*</td>
<td>6.1 ± 1.1‡</td>
<td>5.9 ± 0.9‡</td>
<td>10.4 ± 2.7</td>
</tr>
</tbody>
</table>

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

was observed at 0.015 inspired fraction of halothane (F₁hal), and at 0.02 F₁hal 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 ($\tau$).

Minute ventilation also can be expressed as the product of mean inspiratory flow ($V_{T1}/T_1$) and the duty ratio ($T_1/T_{TOT}$). Halothane administration resulted in a decrease in these two variables. The decrease in $T_1/T_{TOT}$ resulted from a shortening of $T_1$ and a mild and insignificant lengthening of $T_{TOT}$. $T_{TOT}$ 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 F₁hal, respectively.

Mouth occlusion pressure ($P_{EO}$) decreased significantly during halothane administration. A good correlation existed between changes in $V_T/T_1$ and $P_{EO}$ (r = 0.846; P < 0.001). The "effective" impedance of the respiratory system, which is the ratio $P_{EO}/(V_T/T_1)$, 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 F₁hal, respectively.

Diaphragmatic muscle activity during spontaneous breathing also was decreased under halothane anesthesia. Pdi, Pdi, Edi, and the integrated EMG of the diaphragm during an occluded inspiration (Edi)® were significantly decreased (table 2).

The results of Pdi and Edi observed during tetanic stimulations of the phrenic nerve are shown in table 3 and figures 2 and 3. With increasing F₁hal, there was a decrease in Pdi, which was significant even for low frequencies of stimulation. This decrease in Pdi was associated with a parallel decrease in E®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 Pdi 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. Recent experiments in cats have confirmed that halothane depresses the activity of both the phrenic nerve and the inspiratory neurons of the solitary tract nucleus when end-tidal PCO₂ was maintained constant. Halothane also
TABLE 2. Results of Pressure and EMG Indices of Diaphragmatic Function with Increasing Levels of F\textsubscript{hal}, and 30 Min after Halothane Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 9)</th>
<th>0.005 F\textsubscript{hal} (n = 9)</th>
<th>0.01 F\textsubscript{hal} (n = 9)</th>
<th>0.015 F\textsubscript{hal} (n = 7)</th>
<th>0.02 F\textsubscript{hal} (n = 5)</th>
<th>30 Min Recovery (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P) di (cmH_2O)</td>
<td>8.3 ± 1.6</td>
<td>6.3 ± 1.2*</td>
<td>5.2 ± 0.9†</td>
<td>5.4 ± 0.8†</td>
<td>4.7 ± 1.2‡</td>
<td>6.9 ± 1.5*</td>
</tr>
<tr>
<td>(E) di arbitrary units</td>
<td>19.3 ± 3.4</td>
<td>14.4 ± 2.3</td>
<td>12.4 ± 1.0*</td>
<td>12.4 ± 1.3*</td>
<td>9.1 ± 1.8‡</td>
<td>17.4 ± 3.8</td>
</tr>
<tr>
<td>(E^0) di arbitrary units</td>
<td>21.2 ± 2.8</td>
<td>15.9 ± 1.8*</td>
<td>14.3 ± 1.0†</td>
<td>14.2 ± 1.1†</td>
<td>11.7 ± 1.5‡</td>
<td>26.8 ± 4.5</td>
</tr>
</tbody>
</table>

Measurements were performed at end-inspiration \((Pdi, Edi)\), and 200 ms after the onset of an occluded inspiration \((Pd^0, Ed^0)\). * \(P < 0.05\), † \(P < 0.01\), ‡ \(P < 0.001\) when compared with control values.

It has been shown to exert a depressant effect on the sensitivity to carbon dioxide\(^3\) 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 \(V_E\), the authors evaluated the effects of increasing levels of halothane anesthesia on: 1) the diaphragmatic function, by the analysis of \(Edi\) and \(Pdi\) 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 \(Pdi\) and \(Pd^0\). \(Pd^0\) is the response of the phrenic-diaphragm drive to breathing. The changes in \(Pdi\) were associated with a parallel decrease in \(Edi\) 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 \(F_{hal}\) 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 Millar\(^7\) 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.\(^9\)

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 (Pdi) Generated for Various Frequencies of Phrenic Stimulation during Control, for Increasing Levels of F\textsubscript{hal}, and 30 min after Halothane Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>(Pdi 10) Hz ((cmH_2O))</th>
<th>(Pdi 20) Hz ((cmH_2O))</th>
<th>(Pdi 50) Hz ((cmH_2O))</th>
<th>(Pdi 100) Hz ((cmH_2O))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control ((n = 9))</td>
<td>11.9 ± 1.4</td>
<td>21.9 ± 2.0</td>
<td>27.9 ± 2.6</td>
<td>27.9 ± 2.5</td>
</tr>
<tr>
<td>0.005 F\textsubscript{hal} ((n = 9))</td>
<td>10.5 ± 1.2</td>
<td>21.3 ± 2.1</td>
<td>27.4 ± 2.6</td>
<td>28.8 ± 2.8</td>
</tr>
<tr>
<td>0.01 F\textsubscript{hal} ((n = 9))</td>
<td>9.9 ± 1.2*</td>
<td>19.6 ± 2.3*</td>
<td>24.9 ± 2.6*</td>
<td>26.3 ± 2.6*</td>
</tr>
<tr>
<td>0.015 F\textsubscript{hal} ((n = 7))</td>
<td>9.6 ± 0.8*</td>
<td>19.1 ± 1.8*</td>
<td>23.2 ± 2.1†</td>
<td>23.9 ± 2.0‡</td>
</tr>
<tr>
<td>0.02 F\textsubscript{hal} ((n = 5))</td>
<td>7.9 ± 1.4</td>
<td>15.4 ± 2.7*</td>
<td>18.8 ± 3.3†</td>
<td>19.5 ± 3.4†</td>
</tr>
<tr>
<td>Recovery ((n = 7))</td>
<td>10.2 ± 1.4</td>
<td>19.2 ± 2.2*</td>
<td>25.3 ± 2.5*</td>
<td>25.5 ± 2.5†</td>
</tr>
</tbody>
</table>

* \(P < 0.05\), † \(P < 0.01\), ‡ \(P < 0.001\) when compared with control values.
EFFECT OF HALOTHANE ON DIAPHRAGMATIC FUNCTION

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 $F_{\text{hal}}$, 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 50 Hz, 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. 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 $P_{\text{aco}}$, $P_{\text{ao}}$ was significantly decreased with increasing $F_{\text{hal}}$. This decrease can be attributed to the decrease in central neural drive, and to the inhibition of the intercostal motor neurons. The present study shows that the decrease in $P_{\text{ao}}$ 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. 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 $P_{\text{ET}}$ during halothane anesthesia appears to contrast with some previous reports. After halothane administration, Southorn et al. observed a 16.9% decrease in FRC in supine dogs, while after thiopental anesthesia, Lai et al. 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 anesthesia with barbiturates, and remains stable thereafter, when halothane is added.

The absence of periodic inflations of the lungs can induce a decrease in FRC. Mead and Collier 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. 2.** Mean per cent changes in transdiaphragmatic pressure ($P_{\text{di}}$) and in electrical activity of the diaphragm ($E_{\text{di}}$) 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.

**FIG. 3.** Typical record of one dog showing the effects of halothane on transdiaphragmatic pressure ($P_{\text{di}}$) and on the electrical activity of the right ($E_{\text{diR}}$) and left ($E_{\text{diL}}$) 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, $P_{di}$ should be increased; however, in this study $P_{di}$ was decreased. If this decrease in $P_{di}$ 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 $E_{di}$.

$V_T/T_1$ 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, "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. 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**

$T_1/T_{TOT}$ 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. In this study, there was a progressive and significant decrease in $T_1/T_{TOT}$, reaching 67.6 ± 5.2% of the control value at 0.02 F$_{hal}$. This decrease resulted from the shortening of $T_1$ while $T_E$ remained unchanged. In the four dogs that experienced a ventilatory arrest at 0.015 and 0.02 F$_{hal}$, $T_1/T_{TOT}$ 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. noted that at 1.9 MAC halothane, the mean value of $T_1/T_{TOT}$ was 0.259 during oxygen breathing. In the five patients reported by Tusiewicz et al., $T_1/T_{TOT}$ 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 dogs and cats 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$_{hal}$, which usually is observed in humans. The rather elevated value for respiratory frequency during control measurements, although comparable to previous studies and within the reported normal range, 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$_{hal}$ and a decrease in f for higher F$_{hal}$, which ended in respiratory arrest for four dogs. Since within the dogs these effects were observed at different F$_{hal}$, the mean values were increased moderately and insignificantly with F$_{hal}$.

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 $V_E$ observed during halothane administration. Further work is needed to determine the clinical importance of this phenomenon in man.

**References**


2. Ngai SH, Katz RL, Farhie SE: Respiratory effects of trichlorethy-
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3. Tusiewicz K, Bryan AC, Froese AB: Contributions of changing
rib cage-diaphragm interactions to the ventilatory depression
of halothane anesthesia. ANESTHESIOLOGY 47:327–337, 1977
4. Pollard BJ, Millar PA: Potentiating and depressant effects of in-
halation anesthetics on the rat phrenic-diaphragm preparation.
Br J Anaesth 45:404–415, 1973
5. Waud BE, Waud DR: Comparison of the effects of general an-
esthetics on the end-plate of skeletal muscle. ANESTHESIOLOGY
43:540–547, 1975
6. Waud BE, Waud DR: Effects of volatile anesthetics on directly
and indirectly stimulated skeletal muscle. ANESTHESIOLOGY
50:103–110, 1979
7. Rosenberg H: Sites and mechanisms of action of halothane on
skeletal muscle function in vivo. ANESTHESIOLOGY 50:531–
535, 1979
8. Milic-Emili J, Mead J, Turner JM, Glauser FM: Improved tech-
nique for estimating pleural pressure from esophageal balloons.
J Appl Physiol 19:207–211, 1964
9. Aubier M, De Troyer A, Sampson M, Macklem PT, Roussos C:
Aminophylline improves diaphragmatic contractility. N Engl
10. Grassino A, Goldman MD, Mead J, Sears TA: Mechanics of the
human diaphragm during voluntary contraction. J Appl Physiol
44:829–839, 1978
11. Edwards RHT, Young A, Hasking GP, Jones DA: Human skeletal
muscle function: description of tests and normal values. Clin
12. Aubier M, Viives N, Murciano D, Medrano G, Lecocq M, Pari-
ente R: Effects and mechanism of action of terbutaline on
diaphragmatic contractility and fatigue. J Appl Physiol 56:922–
929, 1984
13. Milic-Emili J, Grunstein MM: Drive and timing components of
ventilation. Chest 70(suppl):131–135, 1977
Occulation pressures in men rebreathing CO2 under methoxy-
15. Nishino T, Shira Hata M, Yone Zawa T, Honda Y: Comparison
of changes in the hypoglossal and the phrenic nerve activity
in response to increasing depth of anesthesia in cats. ANESTH-
ESIOLOGY 60:19–24, 1984
16. Tabatabai M, Kitahata LM, Yge O, Matsumoto M, Collins JG:
Effect of halothane on the activity of the inspiratory neurons
of the solitary tract nucleus of the cat (abstract). ANESTHE-
SIOLOGY 59:4492, 1983
17. Knill RL, Gelb AW: Ventilatory responses in hypoxia and hyper-
capnia during halothane sedation and anaesthesia in man.
ANESTHESIOLOGY 49:244–251, 1978
effects of forane and halothane alone and in combination with
19. Grimby L, Hannerz J: Firing rate and recruitment order of toe
extension motor units in different modes of voluntary con-
traction. J Physiol (Lond) 264:865–879, 1977
20. Whitelaw WA, Derenne JPh, Milic-Emili J: Occulsion pressure as
a measure of respiratory centre output in conscious man. Respir
Physiol 23:181–199, 1975
21. Eldridge FL, Vaughn KZ: Relationship of thoracic volume and
airway occlusion pressure muscular effects. J Appl Physiol 43:
312–321, 1977
22. Southorn P, Rehder K, Hyatt RE: Halothane anesthesia and res-
spiratory mechanics in dogs lying supine. J Appl Physiol 49:
300–305, 1980
23. Lai YL, Rodarte JR, Hyatt RE: Respiratory mechanics in recum-
bent dogs anesthetized with thiopental sodium. J Appl Physiol
46:716–720, 1979
24. Hedenstierna G, Lofstrom B, Lundh R: Thoracic gas volume and
chest. Abdomen dimensions during anesthesia and muscle pa-
25. Mead J, Collier C: Relation of volume history of lungs to respiratory
26. Clark JF, Von Euler C: On the regulation of depth and rate of
27. Marsh HM, Rehder K, Hyatt RE: Respiratory timing and depth of
breathing in dogs anesthetized with halothane or enflurane.
28. Mazzarelli M, Haberer JP, Jasparr N, Misroccoli C: Mechanism of
halothane induced tachypnea in cats. ANESTHESIOLOGY 51:
522–527, 1979
29. Berkensbosch A, De Goede J, Olievier CN, Gunder PhH: Sites of
action of halothane on respiratory pattern and ventilatory re-
sponse to CO2 in cats. ANESTHESIOLOGY 57:389–398, 1982
30. Crosfill M, Widdicombe JG: Physical characteristics of the chest
and lungs and the work of breathing in different mammalian
species. J Physiol (Lond) 158:1–14, 1961